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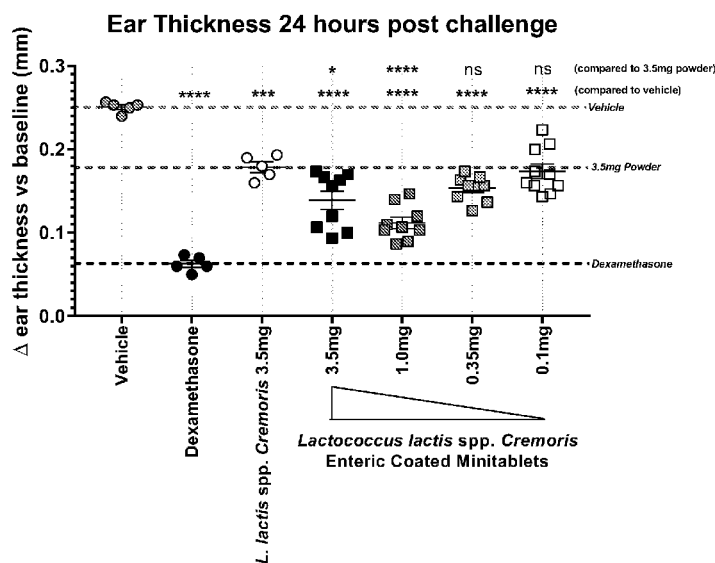
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(54) Title: SOLID DOSAGE FORMS CONTAINING BACTERIA AND MICROBIAL EXTRACELLULAR VESICLES

Figure 1



(57) Abstract: Enterically-coated solid dosage forms containing a pharmaceutical agent which includes bacteria and/or microbial extracellular vesicles (mEVs) are provided. Methods of treatment using such solid dosage forms are also provided.

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SOLID DOSAGE FORMS CONTAINING BACTERIA AND MICROBIAL EXTRACELLULAR VESICLES

Cross-Reference to Related Applications

[0001] This application claims the benefit of U.S. Provisional Application No. 62/954,153, filed on December 27, 2019; the entire contents of said application are incorporated herein in their entirety by this reference.

Summary

[0002] In certain aspects, provided herein are solid dosage forms of a pharmaceutical agent. In certain embodiments, such solid dose forms include capsules, tablets, and minitables. In some embodiments, the capsules, tablets, or minitables are coated with one layer of enteric coating or with two layers of enteric coatings (e.g., an inner enteric coating and an outer enteric coating). In some embodiments, the enterically-coated minitables (with one layer of enteric coating or with two layers of enteric coatings) can be loaded into a capsule.

[0003] Aspects of the disclosure are based, in part, on the discovery that certain solid dosage forms of a pharmaceutical agent provide an increase in therapeutic efficacy and/or physiological effect as compared to other dosage forms of the pharmaceutical agent (e.g., as compared to the same dose of the pharmaceutical agent administered in a form that does not comprise the enteric coating, e.g., a non-enterically coated tablet or non-enterically coated minitab or a suspension of biomass or powder). The solid dosage forms can be formulated to contain a lower dose (e.g., 1/10 or less of a dose) of the pharmaceutical agent than other dosage forms (e.g., as compared to the same dose of the pharmaceutical agent administered in a form that does not comprise the enteric coating, e.g., a non-enterically coated tablet or non-enterically coated minitab or a suspension of biomass or powder), yet result in comparable therapeutic efficacy and/or physiological effect. Such solid dosage forms can alternatively be formulated to contain the same dose of a pharmaceutical agent as other dosage forms (e.g., as compared to the same dose of the pharmaceutical agent administered in a form that does not comprise the enteric coating, e.g., a non-enterically coated tablet or non-enterically coated minitab or a suspension of biomass or powder), yet result in greater therapeutic efficacy or physiological effect (e.g., 10-fold or more therapeutic efficacy or physiological effect). The solid dosage forms of a pharmaceutical

agent as described herein can provide release in the small intestine of the pharmaceutical agent contained therein. The solid dosage forms can be prepared to allow release of the pharmaceutical agent at specific locations in the small intestine. Release of the pharmaceutical agent at particular locations in the small intestine allows the pharmaceutical agent to target and affect cells (e.g., epithelial cells and/or immune cells) located at these specific locations, e.g., which can cause a local effect in the gastrointestinal tract and/or cause a systemic effect (e.g., an effect outside of the gastrointestinal tract).

[0004] In certain embodiments, the solid dosage forms of a pharmaceutical agent as described herein can be used to deliver a variety of pharmaceutical agents that can act on immune cells and/or epithelial cells in the small intestine to cause a systemic effect (e.g., an effect outside of the gastrointestinal tract) and/or can cause a local effect in the gastrointestinal tract.

[0005] In some embodiments, the pharmaceutical agent can be of bacterial origin (e.g., mixture of selected strains or components thereof, such as microbial extracellular vesicles (mEVs) of the mixture of selected strains). The pharmaceutical agent can be of bacterial origin (e.g., a single selected strain and/or components thereof, such as microbial extracellular vesicles (mEVs) of that single selected strain).

[0006] As described herein, improved therapeutic effects were seen with certain solid dosage forms of a pharmaceutical agent that contained one layer of enteric coating, as compared to the same dose of the pharmaceutical agent administered in a form that does not comprise the enteric coating, e.g., a non-enterically coated tablet or non-enterically coated minitabket or a suspension of biomass or powder.

[0007] In some embodiments, a solid dosage form described herein can provide, inter alia, a pharmaceutical agent (e.g., a formulation of a pharmaceutical agent) which enhances the pharmacological potency of the pharmaceutical agent by 10-fold or more in preclinical in vivo models, as compared to the same dose of the pharmaceutical agent administered in a form that does not comprise the enteric coating, e.g., a non-enterically coated tablet or non-enterically coated minitabket or a suspension of biomass or powder). For example, for a given level of therapeutic efficacy and/or physiological effect obtained with a comparator formulation of the pharmaceutical agent, the dose can be reduced (e.g., to 1/10 or less) when prepared in a solid dosage form described herein.

[0008] In some embodiments, or a given dose of a pharmaceutical agent, target engagement (e.g., in the small intestine) can be increased such that for a given dose of a

pharmaceutical agent, target engagement (e.g., in the small intestine) can be increased for better efficacy when the pharmaceutical agent is prepared in a solid dosage form described herein.

[0009] In some aspects, the disclosure provides a solid dosage form (e.g., for oral administration) (e.g., for therapeutic use) comprising a pharmaceutical agent (e.g., a therapeutically effective amount thereof), wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), and wherein the solid dosage form is enterically coated (e.g., comprises an enteric coating; e.g., is coated with an enteric coating).

[0010] In certain embodiments, the solid dosage form comprises a capsule. In some embodiments, the capsule is a size 00, size 0, size 1, size 2, size 3, size 4, or size 5 capsule. In some embodiments, the capsule is a size 0 capsule.

[0011] In some embodiments, the solid dosage form comprises a tablet. In some embodiments, the tablet (e.g., enterically coated tablet) is a 5mm, 6mm, 7mm, 8mm, 9mm, 10mm, 11mm, 12mm, 13mm, 14mm, 15mm, 16mm, 17mm, or 18mm tablet.

[0012] In some embodiments, the solid dosage form comprises a minitab. In some embodiments, the minitab (e.g., enterically coated minitab) is a 1mm minitab, 1.5 mm minitab, 2mm minitab, 3mm minitab, or 4mm minitab. In some embodiments, a plurality of enterically coated minitabs are contained in a capsule (e.g., a size 0 capsule can contain about 31 to about 35 (e.g., 33) minitabs, wherein the minitabs are 3mm in size). In some embodiments, the capsule is a size 00, size 0, size 1, size 2, size 3, size 4, or size 5 capsule. In some embodiments, the capsule comprises HPMC (hydroxyl propyl methyl cellulose) or gelatin.

[0013] In some embodiments, the enteric coating comprises one enteric coating.

[0014] In some embodiments, the enteric coating comprises an inner enteric coating and an outer enteric coating, and wherein the inner and outer enteric coatings are not identical (e.g., the inner and outer enteric coatings do not contain identical components in identical amounts).

[0015] In some embodiments, the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) comprises a polymethacrylate-based copolymer.

[0016] In some embodiments, the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) comprises a methacrylic acid ethyl acrylate (MAE) copolymer (1:1).

[0017] In some embodiments, the one enteric coating comprises methacrylic acid ethyl acrylate (MAE) copolymer (1:1) (such as Kollicoat MAE 100P).

[0018] In some embodiments, the one enteric coating comprises a Eudragit copolymer, e.g., a Eudragit L (e.g., Eudragit L 100-55; Eudragit L 30 D-55), a Eudragit S, a Eudragit RL, a Eudragit RS, a Eudragit E, or a Eudragit FS (e.g., Eudragit FS 30 D).

[0019] In some embodiments, the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) comprises cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), poly(vinyl acetate phthalate) (PVAP), hydroxypropyl methylcellulose phthalate (HPMCP), a fatty acid, a wax, shellac (esters of aleuritic acid), a plastic, a plant fiber, zein, Aqua-Zein (an aqueous zein formulation containing no alcohol), amylose starch, a starch derivative, a dextrin, a methyl acrylate-methacrylic acid copolymer, cellulose acetate succinate, hydroxypropyl methyl cellulose acetate succinate (hypromellose acetate succinate), a methyl methacrylate-methacrylic acid copolymer, or sodium alginate.

[0020] In some embodiments, the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) comprises an anionic polymeric material.

[0021] In some embodiments, the solid dosage form comprises a sub-coat, e.g., under the enteric coating (e.g., one enteric coating). The sub-coat can be used, e.g., to visually mask the appearance of the pharmaceutical agent.

[0022] In some embodiments, the pharmaceutical agent comprises bacteria.

[0023] In some embodiments, the pharmaceutical agent comprises microbial extracellular vesicles (mEV).

[0024] In some embodiments, the pharmaceutical agent comprises bacteria and microbial extracellular vesicles (mEV).

[0025] In some embodiments, the pharmaceutical agent has one or more beneficial immune effects outside the gastrointestinal tract, e.g., when the solid dosage form is orally administered.

[0026] In some embodiments, the pharmaceutical agent modulates immune effects outside the gastrointestinal tract (e.g., outside of the small intestine) in the subject, e.g., when the solid dosage form is orally administered.

[0027] In some embodiments, the pharmaceutical agent causes a systemic effect (e.g., an effect outside of the gastrointestinal tract), e.g., when the solid dosage form is orally administered.

[0028] In some embodiments, the pharmaceutical agent acts on immune cells and/or epithelial cells in the small intestine e.g., causing a systemic effect (e.g., an effect outside of the gastrointestinal tract), e.g., when the solid dosage form is orally administered.

[0029] In some embodiments, the pharmaceutical agent comprises isolated bacteria (e.g., from one or more strains of bacteria (e.g., bacteria of interest) (e.g., a therapeutically effective amount thereof)). E.g., wherein at least 50%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% of the content of the pharmaceutical agent is the isolated bacteria (e.g., bacteria of interest).

[0030] In some embodiments, the pharmaceutical agent comprises bacteria that have been gamma irradiated, UV irradiated, heat inactivated, acid treated, or oxygen sparged.

[0031] In some embodiments, the pharmaceutical agent comprises live bacteria.

[0032] In some embodiments, the pharmaceutical agent comprises dead bacteria.

[0033] In some embodiments, the pharmaceutical agent comprises non-replicating bacteria.

[0034] In some embodiments, the pharmaceutical agent comprises bacteria from one strain of bacteria.

[0035] In some embodiments, the bacteria are lyophilized (e.g., the lyophilized product further comprises a pharmaceutically acceptable excipient) (e.g., a powder form).

[0036] In some embodiments, the bacteria are gamma irradiated.

[0037] In some embodiments, the bacteria are UV irradiated.

[0038] In some embodiments, the bacteria are heat inactivated (e.g., at 50°C for two hours or at 90°C for two hours).

[0039] In some embodiments, the bacteria are acid treated.

[0040] In some embodiments, the bacteria are oxygen sparged (e.g., at 0.1 vvm for two hours).

[0041] In some embodiments, the bacteria are Gram positive bacteria.

- [0042] In some embodiments, the bacteria are Gram negative bacteria.
- [0043] In some embodiments, the bacteria are aerobic bacteria.
- [0044] In some embodiments, the bacteria are anaerobic bacteria. In some embodiments, the anaerobic bacteria comprise obligate anaerobes. In some embodiments, the anaerobic bacteria comprise facultative anaerobes.
- [0045] In some embodiments, the bacteria are acidophile bacteria.
- [0046] In some embodiments, the bacteria are alkaliphile bacteria.
- [0047] In some embodiments, the bacteria are neutralophile bacteria.
- [0048] In some embodiments, the bacteria are fastidious bacteria.
- [0049] In some embodiments, the bacteria are nonfastidious bacteria.
- [0050] In some embodiments, the bacteria are of a taxonomic group (e.g., class, order, family, genus, species or strain) listed in Table 1, Table 2, or Table 3.
- [0051] In some embodiments, the bacteria are a bacterial strain listed in Table 1, Table 2, or Table 3.
- [0052] In some embodiments, the bacteria are of a taxonomic group (e.g., class, order, family, genus, species or strain) listed in Table J.
- [0053] In some embodiments, the bacteria are a bacterial strain listed in Table J.
- [0054] In some embodiments, the Gram negative bacteria belong to class *Negativicutes*.
- [0055] In some embodiments, the Gram negative bacteria belong to family *Veillonellaceae*, *Selenomonadaceae*, *Acidaminococcaceae*, or *Sporomusaceae*.
- [0056] In some embodiments, the bacteria of the genus *Megasphaera*, *Selenomonas*, *Propionospora*, or *Acidaminococcus*.
- [0057] In some embodiments, the bacteria are *Megasphaera sp.*, *Selenomonas felix*, *Acidaminococcus intestine*, or *Propionospora sp.* bacteria.
- [0058] In some embodiments, the bacteria are of the genus *Lactococcus*, *Prevotella*, *Bifidobacterium*, or *Veillonella*.
- [0059] In some embodiments, the bacteria are *Lactococcus lactis cremoris* bacteria.
- [0060] In some embodiments, the bacteria are *Prevotella histicola* bacteria.
- [0061] In some embodiments, the bacteria are *Bifidobacterium animalis* bacteria.
- [0062] In some embodiments, the bacteria are *Veillonella parvula* bacteria.
- [0063] In some embodiments, the bacteria are *Lactococcus lactis cremoris* bacteria. In some embodiments, the *Lactococcus lactis cremoris* bacteria are a strain comprising at

least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the *Lactococcus* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the *Lactococcus* bacteria are *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368).

[0064] In some embodiments, the bacteria are *Prevotella* bacteria. In some embodiments, the *Prevotella* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Prevotella* Strain B 50329 (NRRL accession number B 50329). In some embodiments, the *Prevotella* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Prevotella* Strain B 50329 (NRRL accession number B 50329). In some embodiments, the *Prevotella* bacteria are *Prevotella* Strain B 50329 (NRRL accession number B 50329).

[0065] In some embodiments, the bacteria are *Bifidobacterium* bacteria. In some embodiments, the *Bifidobacterium* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097. In some embodiments, the *Bifidobacterium* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097. In some embodiments, the *Bifidobacterium* bacteria are *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097.

[0066] In some embodiments, the bacteria are *Veillonella* bacteria. In some embodiments, the *Veillonella* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the *Veillonella* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the *Veillonella* bacteria are *Veillonella* bacteria deposited as ATCC designation number PTA-125691.

[0067] In some embodiments, the bacteria are from *Ruminococcus gnavus* bacteria. In some embodiments, the *Ruminococcus gnavus* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695.

[0068] In some embodiments, the bacteria are *Megasphaera sp.* bacteria. In some embodiments, the *Megasphaera sp.* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some embodiments, the *Megasphaera sp.* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some embodiments, the *Megasphaera sp.* bacteria are *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770.

[0069] In some embodiments, the bacteria are *Fournierella massiliensis* bacteria. In some embodiments, the *Fournierella massiliensis* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696.

[0070] In some embodiments, the bacteria are *Harryflintia acetispora* bacteria. In some embodiments, the *Harryflintia acetispora* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide

sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694.

[0071] In some embodiments, the bacteria are of the family *Acidaminococcaceae*, *Alcaligenaceae*, *Akkermansiaceae*, *Bacteriodaceae*, *Bifidobacteriaceae*, *Burkholderiaceae*, *Catabacteriaceae*, *Clostridiaceae*, *Coriobacteriaceae*, *Enterobacteriaceae*, *Enterococcaceae*, *Fusobacteriaceae*, *Lachnospiraceae*, *Listeraceae*, *Mycobacteriaceae*, *Neisseriaceae*, *Odoribacteraceae*, *Oscillospiraceae*, *Peptococcaceae*, *Peptostreptococcaceae*, *Porphyromonadaceae*, *Prevotellaceae*, *Propionibacteraceae*, *Rikenellaceae*, *Ruminococcaceae*, *Selenomonadaceae*, *Sporomusaceae*, *Streptococcaceae*, *Streptomycetaceae*, *Sutterellaceae*, *Synergistaceae*, or *Veillonellaceae*.

[0072] In some embodiments, the bacteria are of the genus *Akkermansia*, *Christensenella*, *Blautia*, *Enterococcus*, *Eubacterium*, *Roseburia*, *Bacteroides*, *Parabacteroides*, or *Erysipelatoclostridium*.

[0073] In some embodiments, the bacteria are *Blautia hydrogenotrophica*, *Blautia stercoris*, *Blautia wexlerae*, *Eubacterium faecium*, *Eubacterium contortum*, *Eubacterium rectale*, *Enterococcus faecalis*, *Enterococcus durans*, *Enterococcus villorum*, *Enterococcus gallinarum*; *Bifidobacterium lactis*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, *Bifidobacterium animalis*, or *Bifidobacterium breve* bacteria.

[0074] In some embodiments, the bacteria are *BCG (bacillus Calmette-Guerin)*, *Parabacteroides*, *Blautia*, *Veillonella*, *Lactobacillus salivarius*, *Agathobaculum*, *Ruminococcus gnavus*, *Paraclostridium benzoelyticum*, *Turicibacter sanguinus*, *Burkholderia*, *Klebsiella quasipneumoniae ssp similpneumoniae*, *Klebsiella oxytoca*, *Tyzzera nexilis*, or *Neisseria* bacteria.

[0075] In some embodiments, the bacteria are *Blautia hydrogenotrophica* bacteria.

[0076] In some embodiments, the bacteria are *Blautia stercoris* bacteria.

[0077] In some embodiments, the bacteria are *Blautia wexlerae* bacteria.

[0078] In some embodiments, the bacteria are *Enterococcus gallinarum* bacteria.

[0079] In some embodiments, the bacteria are *Enterococcus faecium* bacteria.

[0080] In some embodiments, the bacteria are *Bifidobacterium bifidum* bacteria.

[0081] In some embodiments, the bacteria are *Bifidobacterium breve* bacteria.

[0082] In some embodiments, the bacteria are *Bifidobacterium longum* bacteria.

[0083] In some embodiments, the bacteria are *Roseburia hominis* bacteria.

- [0084] In some embodiments, the bacteria are *Bacteroides thetaiotaomicron* bacteria.
- [0085] In some embodiments, the bacteria are *Bacteroides coprocola* bacteria.
- [0086] In some embodiments, the bacteria are *Erysipelatoclostridium ramosum* bacteria.
- [0087] In some embodiments, the bacteria are *Megasphaera massiliensis* bacteria.
- [0088] In some embodiments, the bacteria are *Eubacterium* bacteria.
- [0089] In some embodiments, the bacteria are *Parabacteroides distasonis* bacteria.
- [0090] In some embodiments, the bacteria are *Lactobacillus plantarum* bacteria.
- [0091] In some embodiments, the bacteria are bacteria of the *Negativicutes* class.
- [0092] In some embodiments, the bacteria are of the *Veillonellaceae* family.
- [0093] In some embodiments, the bacteria are of the *Selenomonadaceae* family.
- [0094] In some embodiments, the bacteria are of the *Acidaminococcaceae* family.
- [0095] In some embodiments, the bacteria are of the *Sporomusaceae* family.
- [0096] In some embodiments, the bacteria are of the *Megasphaera* genus.
- [0097] In some embodiments, the bacteria are of the *Selenomonas* genus.
- [0098] In some embodiments, the bacteria are of the *Propionospora* genus.
- [0099] In some embodiments, the bacteria are of the *Acidaminococcus* genus.
- [0100] In some embodiments, the bacteria are *Megasphaera* sp. bacteria.
- [0101] In some embodiments, the bacteria are *Selenomonas felix* bacteria.
- [0102] In some embodiments, the bacteria are *Acidaminococcus intestini* bacteria.
- [0103] In some embodiments, the bacteria are *Propionospora* sp. bacteria.
- [0104] In some embodiments, the bacteria are bacteria of the *Clostridia* class.
- [0105] In some embodiments, the bacteria are of the *Oscillospiraceae* family.
- [0106] In some embodiments, the bacteria are of the *Faecalibacterium* genus.
- [0107] In some embodiments, the bacteria are of the *Fournierella* genus.
- [0108] In some embodiments, the bacteria are of the *Harryflintia* genus.
- [0109] In some embodiments, the bacteria are of the *Agathobaculum* genus.
- [0110] In some embodiments, the bacteria are *Faecalibacterium prausnitzii* (e.g., *Faecalibacterium prausnitzii* Strain A) bacteria.
- [0111] In some embodiments, the bacteria are *Fournierella massiliensis* (e.g., *Fournierella massiliensis* Strain A) bacteria.

[0112] In some embodiments, the bacteria are *Harryflintia acetispora* (e.g., *Harryflintia acetispora* Strain A) bacteria.

[0113] In some embodiments, the bacteria are *Agathobaculum sp.* (e.g., *Agathobaculum sp.* Strain A) bacteria.

[0114] In some embodiments, the bacteria are a strain of *Agathobaculum sp.* In some embodiments, the *Agathobaculum sp.* strain is a strain comprising at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity (e.g., at least 99.5% sequence identity, at least 99.6% sequence identity, at least 99.7% sequence identity, at least 99.8% sequence identity, at least 99.9% sequence identity) to the nucleotide sequence (e.g., genomic sequence, 16S sequence, CRISPR sequence) of the *Agathobaculum sp.* Strain A (ATCC Deposit Number PTA-125892). In some embodiments, the *Agathobaculum sp.* strain is the *Agathobaculum sp.* Strain A (ATCC Deposit Number PTA-125892).

[0115] In some embodiments, the bacteria are of the class *Bacteroidia* [phylum *Bacteroidota*]. In some embodiments, the bacteria are of order *Bacteroidales*. In some embodiments, the bacteria are of the family *Porphyromonadaceae*. In some embodiments, the bacteria are of the family *Prevotellaceae*. In some embodiments, the bacteria are of the class *Bacteroidia* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the bacteria are of the class *Bacteroidia* that stain Gram negative. In some embodiments, the bacteria are of the class *Bacteroidia* wherein the bacteria is diderm and the bacteria stain Gram negative.

[0116] In some embodiments, the bacteria are of the class *Clostridia* [phylum *Firmicutes*]. In some embodiments, the bacteria are of the order *Eubacteriales*. In some embodiments, the bacteria are of the family *Oscillispiraceae*. In some embodiments, the bacteria are of the family *Lachnospiraceae*. In some embodiments, the bacteria are of the family *Peptostreptococcaceae*. In some embodiments, the bacteria are of the family *Clostridiales family XIII/ Incertae sedis 41*. In some embodiments, the bacteria are of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm. In some embodiments, the bacteria are of the class *Clostridia* that stain Gram negative. In some embodiments, the bacteria are of the class *Clostridia* that stain Gram positive. In some embodiments, the bacteria are of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram negative. In some embodiments, the

bacteria are of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram positive.

[0117] In some embodiments, the bacteria are of the class *Negativicutes* [phylum *Firmicutes*]. In some embodiments, the bacteria are of the order *Veillonellales*. In some embodiments, the bacteria are of the family *Veillonelloceae*. In some embodiments, the bacteria are of the order *Selenomonadales*. In some embodiments, the bacteria are of the family *Selenomonadaceae*. In some embodiments, the bacteria are of the family *Sporomusaceae*. In some embodiments, the bacteria are of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the bacteria are of the class *Negativicutes* that stain Gram negative. In some embodiments, the bacteria are of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[0118] In some embodiments, the bacteria are of the class *Synergistia* [phylum *Synergistota*]. In some embodiments, the bacteria are of the order *Synergistales*. In some embodiments, the bacteria are of the family *Synergistaceae*. In some embodiments, the bacteria are of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the bacteria are of the class *Synergistia* that stain Gram negative. In some embodiments, the bacteria are of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[0119] In some embodiments, the bacteria are bacteria that produce metabolites, e.g., the bacteria produce butyrate, iosine, propionate, or tryptophan metabolites.

[0120] In some embodiments, the bacteria produce butyrate. In some embodiments, the bacteria are from the genus *Blautia*; *Christensella*; *Copracoccus*; *Eubacterium*; *Lachnospiraceae*; *Megasphaera*; or *Roseburia*.

[0121] In some embodiments, the bacteria produce iosine. In some embodiments, the bacteria are from the genus *Bifidobacterium*; *Lactobacillus*; or *Olsenella*.

[0122] In some embodiments, the bacteria produce propionate. In some embodiments, the bacteria are from the genus *Akkermansia*; *Bacteriodes*; *Dialister*; *Eubacterium*; *Megasphaera*; *Parabacteriodes*; *Prevotella*; *Ruminococcus*; or *Veillonella*.

[0123] In some embodiments, the bacteria produce tryptophan metabolites. In some embodiments, the bacteria are from the genus *Lactobacillus* or *Peptostreptococcus*.

[0124] In some embodiments, the bacteria are bacteria that produce inhibitors of histone deacetylase 3 (HDAC3). In some embodiments, the bacteria are from the species

Bariatricus massiliensis, *Faecalibacterium prausnitzii*, *Megasphaera massiliensis* or *Roseburia intestinalis*.

[0125] In some embodiments, the pharmaceutical agent comprises isolated mEVs (e.g., from one or more strains of bacteria (e.g., bacteria of interest)) (e.g., a therapeutically effective amount thereof). E.g., wherein at least 50%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% of the content of the pharmaceutical agent is isolated mEV of bacteria (e.g., bacteria of interest).

[0126] In some embodiments, the pharmaceutical agent comprises mEVs and the mEVs comprise secreted mEVs (smEVs).

[0127] In some embodiments, the pharmaceutical agent comprises mEVs and the mEVs comprise processed mEVs (pmEVs).

[0128] In some embodiments, the pharmaceutical agent comprises pmEVs and the pmEVs are produced from bacteria that have been gamma irradiated, UV irradiated, heat inactivated, acid treated, or oxygen sparged.

[0129] In some embodiments, the pharmaceutical agent comprises pmEVs and the pmEVs are produced from live bacteria.

[0130] In some embodiments, the pharmaceutical agent comprises pmEVs and the pmEVs are produced from dead bacteria.

[0131] In some embodiments, the pharmaceutical agent comprises pmEVs and the pmEVs are produced from non-replicating bacteria.

[0132] In some embodiments, the pharmaceutical agent comprises mEVs and the mEVs are from one strain of bacteria.

[0133] In some embodiments, the mEVs are lyophilized (e.g., the lyophilized product further comprises a pharmaceutically acceptable excipient).

[0134] In some embodiments, the mEVs are gamma irradiated.

[0135] In some embodiments, the mEVs are UV irradiated.

[0136] In some embodiments, the mEVs are heat inactivated (e.g., at 50°C for two hours or at 90°C for two hours).

[0137] In some embodiments, the mEVs are acid treated.

[0138] In some embodiments, the mEVs are oxygen sparged (e.g., at 0.1 vvm for two hours).

[0139] In some embodiments, the mEVs are from Gram positive bacteria.

[0140] In some embodiments, the mEVs are from Gram negative bacteria.

- [0141] In some embodiments, the mEVs are from aerobic bacteria.
- [0142] In some embodiments, the mEVs are from anaerobic bacteria. In some embodiments, the anaerobic bacteria comprise obligate anaerobes. In some embodiments, the anaerobic bacteria comprise facultative anaerobes.
- [0143] In some embodiments, the mEVs are from acidophile bacteria.
- [0144] In some embodiments, the mEVs are from alkaliphile bacteria.
- [0145] In some embodiments, the mEVs are from neutralophile bacteria.
- [0146] In some embodiments, the mEVs are from fastidious bacteria.
- [0147] In some embodiments, the mEVs are from nonfastidious bacteria.
- [0148] In some embodiments, the mEVs are from bacteria of a taxonomic group (e.g., class, order, family, genus, species or strain) listed in Table 1, Table 2, or Table 3.
- [0149] In some embodiments, the mEVs are from a bacterial strain listed in Table 1, Table 2, or Table 3.
- [0150] In some embodiments, the mEVs are from bacteria of a taxonomic group (e.g., class, order, family, genus, species or strain) listed in Table J.
- [0151] In some embodiments, the mEVs are from a bacterial strain listed in Table J.
- [0152] In some embodiments, the Gram negative bacteria belong to class *Negativicutes*.
- [0153] In some embodiments, the Gram negative bacteria belong to family *Veillonellaceae*, *Selenomonadaceae*, *Acidaminococcaceae*, or *Sporomusaceae*.
- [0154] In some embodiments, the mEVs are from bacteria of the genus *Megasphaera*, *Selenomonas*, *Propionospora*, or *Acidaminococcus*.
- [0155] In some embodiments, the mEVs are *Megasphaera sp.*, *Selenomonas felix*, *Acidaminococcus intestine*, or *Propionospora sp.* bacteria.
- [0156] In some embodiments, the mEVs are from bacteria of the genus *Lactococcus*, *Prevotella*, *Bifidobacterium*, or *Veillonella*.
- [0157] In some embodiments, the mEVs are from *Lactococcus lactis cremoris* bacteria.
- [0158] In some embodiments, the mEVs are from *Prevotella histicola* bacteria.
- [0159] In some embodiments, the mEVs are from *Bifidobacterium animalis* bacteria.
- [0160] In some embodiments, the mEVs are from *Veillonella parvula* bacteria.

[0161] In some embodiments, the mEVs are from *Lactococcus lactis cremoris* bacteria. In some embodiments, the *Lactococcus lactis cremoris* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the *Lactococcus* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the *Lactococcus* bacteria are from *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368).

[0162] In some embodiments, the mEVs are from *Prevotella* bacteria. In some embodiments, the *Prevotella* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Prevotella* Strain B 50329 (NRRL accession number B 50329). In some embodiments, the *Prevotella* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Prevotella* Strain B 50329 (NRRL accession number B 50329). In some embodiments, the *Prevotella* bacteria are from *Prevotella* Strain B 50329 (NRRL accession number B 50329).

[0163] In some embodiments, the mEVs are from *Bifidobacterium* bacteria. In some embodiments, the *Bifidobacterium* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097. In some embodiments, the *Bifidobacterium* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097. In some embodiments, the *Bifidobacterium* bacteria are from *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097.

[0164] In some embodiments, the mEVs are from *Veillonella* bacteria. In some embodiments, the *Veillonella* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the *Veillonella* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the

Veillonella bacteria are from *Veillonella* bacteria deposited as ATCC designation number PTA-125691.

[0165] In some embodiments, the mEVs are from *Ruminococcus gnavus* bacteria. In some embodiments, the *Ruminococcus gnavus* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are from *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695.

[0166] In some embodiments, the mEVs are from *Megasphaera sp.* bacteria. In some embodiments, the *Megasphaera sp.* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some embodiments, the *Megasphaera sp.* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some embodiments, the *Megasphaera sp.* bacteria are from *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770.

[0167] In some embodiments, the mEVs are from *Fournierella massiliensis* bacteria. In some embodiments, the *Fournierella massiliensis* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are from *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696.

[0168] In some embodiments, the mEVs are from *Harryflintia acetispora* bacteria. In some embodiments, the *Harryflintia acetispora* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the

nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are from *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694.

[0169] In some embodiments, the mEVs are from bacteria of the family *Acidaminococcaceae*, *Alcaligenaceae*, *Akkermansiaceae*, *Bacteriodaceae*, *Bifidobacteriaceae*, *Burkholderiaceae*, *Catabacteriaceae*, *Clostridiaceae*, *Coriobacteriaceae*, *Enterobacteriaceae*, *Enterococcaceae*, *Fusobacteriaceae*, *Lachnospiraceae*, *Listeraceae*, *Mycobacteriaceae*, *Neisseriaceae*, *Odoribacteraceae*, *Oscillospiraceae*, *Peptococcaceae*, *Peptostreptococcaceae*, *Porphyromonadaceae*, *Prevotellaceae*, *Propionibacteraceae*, *Rikenellaceae*, *Ruminococcaceae*, *Selenomonadaceae*, *Sporomusaceae*, *Streptococcaceae*, *Streptomyetaceae*, *Sutterellaceae*, *Synergistaceae*, or *Veillonellaceae*.

[0170] In some embodiments, the mEVs are from bacteria of the genus *Akkermansia*, *Christensenella*, *Blautia*, *Enterococcus*, *Eubacterium*, *Roseburia*, *Bacteroides*, *Parabacteroides*, or *Erysipelatoclostridium*.

[0171] In some embodiments, the mEVs are from *Blautia hydrogenotrophica*, *Blautia stercoris*, *Blautia wexlerae*, *Eubacterium faecium*, *Eubacterium contortum*, *Eubacterium rectale*, *Enterococcus faecalis*, *Enterococcus durans*, *Enterococcus villorum*, *Enterococcus gallinarum*; *Bifidobacterium lactis*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, *Bifidobacterium animalis*, or *Bifidobacterium breve* bacteria.

[0172] In some embodiments, the mEVs are from *BCG (bacillus Calmette-Guerin)*, *Parabacteroides*, *Blautia*, *Veillonella*, *Lactobacillus salivarius*, *Agathobaculum*, *Ruminococcus gnavus*, *Paraclostridium benzoelyticum*, *Turicibacter sanguinus*, *Burkholderia*, *Klebsiella quasipneumoniae ssp similpneumoniae*, *Klebsiella oxytoca*, *Tyzzerelex nexilis*, or *Neisseria* bacteria.

[0173] In some embodiments, the mEVs are from *Blautia hydrogenotrophica* bacteria.

[0174] In some embodiments, the mEVs are from *Blautia stercoris* bacteria.

[0175] In some embodiments, the mEVs are from *Blautia wexlerae* bacteria.

- [0176] In some embodiments, the mEVs are from *Enterococcus gallinarum* bacteria.
- [0177] In some embodiments, the mEVs are from *Enterococcus faecium* bacteria.
- [0178] In some embodiments, the mEVs are from *Bifidobacterium bifidum* bacteria.
- [0179] In some embodiments, the mEVs are from *Bifidobacterium breve* bacteria.
- [0180] In some embodiments, the mEVs are from *Bifidobacterium longum* bacteria.
- [0181] In some embodiments, the mEVs are from *Roseburia hominis* bacteria.
- [0182] In some embodiments, the mEVs are from *Bacteroides thetaiotaomicron* bacteria.
- [0183] In some embodiments, the mEVs are from *Bacteroides coprocola* bacteria.
- [0184] In some embodiments, the mEVs are from *Erysipelatoclostridium ramosum* bacteria.
- [0185] In some embodiments, the mEVs are from *Megasphaera massiliensis* bacteria.
- [0186] In some embodiments, the mEVs are from *Eubacterium* bacteria.
- [0187] In some embodiments, the mEVs are from *Parabacteroides distasonis* bacteria.
- [0188] In some embodiments, the mEVs are from *Lactobacillus plantarum* bacteria.
- [0189] In some embodiments, the mEVs are from bacteria of the *Negativicutes* class.
- [0190] In some embodiments, the mEVs are from bacteria of the *Veillonellaceae* family.
- [0191] In some embodiments, the mEVs are from bacteria of the *Selenomonadaceae* family.
- [0192] In some embodiments, the mEVs are from bacteria of the *Acidaminococcaceae* family.
- [0193] In some embodiments, the mEVs are from bacteria of the *Sporomusaceae* family.
- [0194] In some embodiments, the mEVs are from bacteria of the *Megasphaera* genus.
- [0195] In some embodiments, the mEVs are from bacteria of the *Selenomonas* genus.

- [0196] In some embodiments, the mEVs are from bacteria of the *Propionospora* genus.
- [0197] In some embodiments, the mEVs are from bacteria of the *Acidaminococcus* genus.
- [0198] In some embodiments, the mEVs are from *Megasphaera sp.* bacteria.
- [0199] In some embodiments, the mEVs are from *Selenomonas felix* bacteria.
- [0200] In some embodiments, the mEVs are from *Acidaminococcus intestini* bacteria.
- [0201] In some embodiments, the mEVs are from *Propionospora sp.* bacteria.
- [0202] In some embodiments, the mEVs are from bacteria of the *Clostridia* class.
- [0203] In some embodiments, the mEVs are from bacteria of the *Oscillospiraceae* family.
- [0204] In some embodiments, the mEVs are from bacteria of the *Faecalibacterium* genus.
- [0205] In some embodiments, the mEVs are from bacteria of the *Fournierella* genus.
- [0206] In some embodiments, the mEVs are from bacteria of the *Harryflintia* genus.
- [0207] In some embodiments, the mEVs are from bacteria of the *Agathobaculum* genus.
- [0208] In some embodiments, the mEVs are from *Faecalibacterium prausnitzii* (e.g., *Faecalibacterium prausnitzii* Strain A) bacteria.
- [0209] In some embodiments, the mEVs are from *Fournierella massiliensis* (e.g., *Fournierella massiliensis* Strain A) bacteria.
- [0210] In some embodiments, the mEVs are from *Harryflintia acetispora* (e.g., *Harryflintia acetispora* Strain A) bacteria.
- [0211] In some embodiments, the mEVs are from *Agathobaculum sp.* (e.g., *Agathobaculum sp.* Strain A) bacteria.
- [0212] In some embodiments, the mEVs are from a strain of *Agathobaculum sp.* In some embodiments, the *Agathobaculum sp.* strain is a strain comprising at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity (e.g., at least 99.5% sequence identity, at least 99.6% sequence identity, at least 99.7% sequence identity, at least 99.8% sequence identity, at least 99.9% sequence identity) to the nucleotide sequence (e.g., genomic sequence, 16S sequence, CRISPR sequence) of the *Agathobaculum sp.*

Strain A (ATCC Deposit Number PTA-125892). In some embodiments, the *Agathobaculum* sp. strain is the *Agathobaculum* sp. Strain A (ATCC Deposit Number PTA-125892).

[0213] In some embodiments, the mEVs are from bacteria of the class *Bacteroidia* [phylum *Bacteroidota*]. In some embodiments, the mEVs are from bacteria of order *Bacteroidales*. In some embodiments, the mEVs are from bacteria of the family *Porphyromonadaceae*. In some embodiments, the mEVs are from bacteria of the family *Prevotellaceae*. In some embodiments, the mEVs are from bacteria of the class *Bacteroidia* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the mEVs are from bacteria of the class *Bacteroidia* that stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Bacteroidia* wherein the bacteria is diderm and the bacteria stain Gram negative.

[0214] In some embodiments, the mEVs are from bacteria of the class *Clostridia* [phylum *Firmicutes*]. In some embodiments, the mEVs are from bacteria of the order *Eubacteriales*. In some embodiments, the mEVs are from bacteria of the family *Oscillispiraceae*. In some embodiments, the mEVs are from bacteria of the family *Lachnospiraceae*. In some embodiments, the mEVs are from bacteria of the family *Peptostreptococcaceae*. In some embodiments, the mEVs are from bacteria of the family *Clostridiales* family *XIII/ Incertae sedis 41*. In some embodiments, the mEVs are from bacteria of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm. In some embodiments, the mEVs are from bacteria of the class *Clostridia* that stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Clostridia* that stain Gram positive. In some embodiments, the mEVs are from bacteria of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram positive.

[0215] In some embodiments, the mEVs are from bacteria of the class *Negativicutes* [phylum *Firmicutes*]. In some embodiments, the mEVs are from bacteria of the order *Veillonellales*. In some embodiments, the mEVs are from bacteria of the family *Veillonelloceae*. In some embodiments, the mEVs are from bacteria of the order *Selenomonadales*. In some embodiments, the mEVs are from bacteria of the family *Selenomonadaceae*. In some embodiments, the mEVs are from bacteria of the family

Sporomusaceae. In some embodiments, the mEVs are from bacteria of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the mEVs are from bacteria of the class *Negativicutes* that stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[0216] In some embodiments, the mEVs are from bacteria of the class *Synergistia* [phylum *Synergistota*]. In some embodiments, the mEVs are from bacteria of the order *Synergistales*. In some embodiments, the mEVs are from bacteria of the family *Synergistaceae*. In some embodiments, the mEVs are from bacteria of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the mEVs are from bacteria of the class *Synergistia* that stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[0217] In some embodiments, the mEVs are from bacteria that produce metabolites, e.g., the bacteria produce butyrate, iosine, propionate, or tryptophan metabolites.

[0218] In some embodiments, the bacteria produce butyrate. In some embodiments, the bacteria are from the genus *Blautia*; *Christensella*; *Copracoccus*; *Eubacterium*; *Lachnospiraceae*; *Megasphaera*; or *Roseburia*.

[0219] In some embodiments, the bacteria produce iosine. In some embodiments, the bacteria are from the genus *Bifidobacterium*; *Lactobacillus*; or *Olsenella*.

[0220] In some embodiments, the bacteria produce propionate. In some embodiments, the bacteria are from the genus *Akkermansia*; *Bacteriodes*; *Dialister*; *Eubacterium*; *Megasphaera*; *Parabacteriodes*; *Prevotella*; *Ruminococcus*; or *Veillonella*.

[0221] In some embodiments, the bacteria produce tryptophan metabolites. In some embodiments, the bacteria are from the genus *Lactobacillus* or *Peptostreptococcus*.

[0222] In some embodiments, the mEVs are from bacteria that produce inhibitors of histone deacetylase 3 (HDAC3). In some embodiments, the bacteria are from the species *Bariatricus massiliensis*, *Faecalibacterium prausnitzii*, *Megasphaera massiliensis* or *Roseburia intestinalis*.

[0223] In some embodiments, the pharmaceutical agent comprises bacteria and the dose of bacteria is about 1×10^7 to about 2×10^{12} (e.g., about 3×10^{10} or about 1.5×10^{11} or about 1.5×10^{12}) cells (e.g., wherein cell number is determined by total cell count, which is

determined by Coulter counter), wherein the dose is per capsule or tablet or per total number of minitabets in a capsule. In some embodiments, the pharmaceutical agent comprises bacteria and the dose of bacteria is about 1×10^{10} to about 2×10^{12} (e.g., about 1.6×10^{11} or about 8×10^{11} or about 9.6×10^{11} or about 12.8×10^{11} or about 1.6×10^{12}) cells (e.g., wherein cell number is determined by total cell count, e.g., as determined by Coulter counter), wherein the dose is per capsule or tablet or per total number of minitabets in a capsule.

[0224] In some embodiments, the pharmaceutical agent comprises bacteria and the dose of bacteria is about 1×10^9 , about 3×10^9 , about 5×10^9 , about 1.5×10^{10} , about 3×10^{10} , about 5×10^{10} , about 1.5×10^{11} , about 1.5×10^{12} , or about 2×10^{12} cells, wherein the dose is per capsule or tablet or per total number of minitabets in a capsule.

[0225] In some embodiments, the pharmaceutical agent comprises mEVs and the dose of mEVs is about 1×10^5 to about 7×10^{13} particles (e.g., wherein particle count is determined by NTA (nanoparticle tracking analysis)), wherein the dose is per capsule or tablet or per total number of minitabets in a capsule. In some embodiments, the pharmaceutical agent comprises mEVs and the dose of mEVs is about 1×10^{10} to about 7×10^{13} particles (e.g., wherein particle count is determined by NTA (nanoparticle tracking analysis)), wherein the dose is per capsule or tablet or per total number of minitabets in a capsule.

[0226] In some embodiments, the pharmaceutical agent comprises bacteria and/or mEVs and the dose of the pharmaceutical agent (e.g., bacteria and/or mEVs) is about 10 mg to about 3500 mg, wherein the dose is per capsule or tablet or per total number of minitabets in a capsule.

[0227] In some embodiments, the pharmaceutical agent comprises bacteria and/or mEVs and the dose of the pharmaceutical agent (e.g., bacteria and/or mEVs) is about 30 mg to about 1300 mg (by weight of bacteria and/or mEVs) (about 25, about 30, about 35, about 50, about 75, about 100, about 120, about 150, about 250, about 300, about 350, about 400, about 500, about 600, about 700, about 750, about 800, about 900, about 1000, about 1100, about 1200, about 1250, about 1300, about 2000, about 2500, about 3000, or about 3500 mg wherein the dose is per capsule or tablet or per total number of minitabets in a capsule.

[0228] In some embodiments, the pharmaceutical agent comprises bacteria and/or mEVs and the dose of pharmaceutical agent (e.g., bacteria and/or mEVs) is about 2×10^6 to about 2×10^{16} particles (e.g., wherein particle count is determined by NTA (nanoparticle

tracking analysis)), wherein the dose is per capsule or tablet or per total number of minitabets in a capsule.

[0229] In some embodiments, the pharmaceutical agent comprises bacteria and/or mEVs and the dose of pharmaceutical agent (e.g., bacteria and/or mEVs) is about 5 mg to about 900 mg total protein (e.g., wherein total protein is determined by Bradford assay or BCA), wherein the dose is per capsule or tablet or per total number of minitabets in a capsule.

[0230] In some embodiments, the solid dosage form further comprises one or more additional pharmaceutical agents.

[0231] In some embodiments, the solid dosage form further comprises an excipient (e.g., an excipient described herein, e.g., a diluent, a binder and/or an adhesive, a disintegrant, a lubricant and/or a glidant, a coloring agent, a flavoring agent, and/or a sweetening agent).

[0232] In some aspects, the disclosure provides a method of treating a subject (e.g., human) (e.g., a subject in need of treatment), the method comprising:

[0233] administering to the subject a solid dosage form, wherein the solid dosage form comprises a pharmaceutical agent (e.g., a therapeutically effective amount thereof), wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), and wherein the solid dosage form is enterically coated (e.g., comprises an enteric coating; e.g., is coated with an enteric coating).

[0234] In some aspects, the disclosure provides a solid dosage form for use in treating a subject (e.g., human) (e.g., a subject in need of treatment), wherein the solid dosage form comprises a pharmaceutical agent (e.g., a therapeutically effective amount thereof), wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), and wherein the solid dosage form is enterically coated (e.g., comprises an enteric coating; e.g., is coated with an enteric coating).

[0235] In some aspects, the disclosure provides use of a solid dosage form for the preparation of a medicament for treating a subject (e.g., human) (e.g., a subject in need of treatment), wherein the solid dosage form comprises a pharmaceutical agent (e.g., a therapeutically effective amount thereof), wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), and wherein the solid dosage form is enterically coated (e.g., comprises an enteric coating; e.g., is coated with an enteric coating).

[0236] In some embodiments, the solid dosage form is orally administered (e.g., is for oral administration).

[0237] In some embodiments, the solid dosage form (e.g., a capsule, a tablet, or a plurality of minitables (e.g., contained in a capsule)) is administered (e.g., is for administration) 1, 2, 3, or 4 times a day.

[0238] In some embodiments, the solid dosage form comprises a capsule, a tablet, or a plurality of minitables (e.g., contained in a capsule) and 1, 2, 3, or 4 solid dosage forms (e.g., a capsule, a tablet, or a plurality of minitables (e.g., contained in a capsule)) are administered (e.g., are for administration) 1, 2, 3, or 4 times a day.

[0239] In some embodiments, the solid dosage form provides an increase in efficacy or in physiological effect of the pharmaceutical agent (e.g., 10-fold or more) as compared to other dosage forms (e.g., as compared to the same dose of the pharmaceutical agent administered in a form that does not comprise the enteric coating, e.g., a non-enterically coated tablet or non-enterically coated minitab or a suspension of biomass or powder).

[0240] In some embodiments, the solid dosage form provides release in the small intestine of the pharmaceutical agent contained in the solid dosage form.

[0241] In some embodiments, the solid dosage form delivers the pharmaceutical agent to the small intestine, wherein the pharmaceutical agent can act on immune cells and/or epithelial cells in the small intestine, e.g., to cause a systemic effect (e.g., an effect outside of the gastrointestinal tract).

[0242] In some embodiments, the solid dosage form provides increased efficacy or increased physiological effect (10-fold or more increased efficacy) (e.g., as measured by a systemic effect (e.g., outside of the gastrointestinal tract) of the pharmaceutical agent, e.g., in ear thickness in DTH model for inflammation; tumor size in cancer model), e.g., as compared to the same dose of the pharmaceutical agent administered in a form that does not comprise the enteric coating, e.g., a suspension or non-enterically coated tablet or non-enterically coated minitab).

[0243] In some embodiments, the pharmaceutical agent provides one or more beneficial immune effects outside the gastrointestinal tract (e.g., outside of the small intestine), e.g., when orally administered.

[0244] In some embodiments, the pharmaceutical agent modulates immune effects outside the gastrointestinal tract (e.g., outside of the small intestine) in the subject, e.g., when orally administered.

[0245] In some embodiments, the pharmaceutical agent causes a systemic effect (e.g., an effect outside of the gastrointestinal tract), e.g., when orally administered.

[0246] In some embodiments, the pharmaceutical agent acts on immune cells and/or epithelial cells in the small intestine (e.g., causing a systemic effect (e.g., an effect outside of the gastrointestinal tract)), e.g., when orally administered.

[0247] In some embodiments, the solid dosage form is administered orally and has one or more beneficial immune effects outside the gastrointestinal tract (e.g., interaction between the pharmaceutical agent and cells in the small intestine modulates a systemic immune response).

[0248] In some embodiments, the solid dosage form is administered orally and modulates immune effects outside the gastrointestinal tract (e.g., interaction between agent and cells in the small intestine modulates a systemic immune response).

[0249] In some embodiments, the solid dosage form is administered orally and activates innate antigen presenting cells (e.g., in the small intestine).

[0250] In some embodiments, the subject is in need of treatment (and/or prevention) of a cancer.

[0251] In some embodiments, the subject is in need of treatment (and/or prevention) of an autoimmune disease.

[0252] In some embodiments, the subject is in need of treatment (and/or prevention) of an inflammatory disease.

[0253] In some embodiments, the subject is in need of treatment (and/or prevention) of a metabolic disease.

[0254] In some embodiments, the subject is in need of treatment (and/or prevention) of dysbiosis.

[0255] In some embodiments, the solid dosage form is administered in combination with an additional pharmaceutical agent.

[0256] In certain embodiments, the solid dosage form comprises a capsule. In some embodiments, the capsule is a size 00, size 0, size 1, size 2, size 3, size 4, or size 5 capsule. In some embodiments, the capsule is a size 0 capsule.

[0257] In some embodiments, the solid dosage form comprises a tablet. In some embodiments, the tablet (e.g., enterically coated tablet) is a 5mm, 6mm, 7mm, 8mm, 9mm, 10mm, 11mm, 12mm, 13mm, 14mm, 15mm, 16mm, 17mm, or 18mm tablet.

[0258] In some embodiments, the solid dosage form comprises a minitabket. In some embodiments, the minitabket (e.g., enterically coated minitabket) is a 1mm minitabket, 1.5 mm minitabket, 2mm minitabket, 3mm minitabket, or 4mm minitabket. In some embodiments, a plurality of enterically coated minitabkets are contained in a capsule (e.g., a size 0 capsule can contain about 31 to about 35 (e.g., 33) minitabkets, wherein the minitabkets are 3mm in size). In some embodiments, the capsule is a size 00, size 0, size 1, size 2, size 3, size 4, or size 5 capsule. In some embodiments, the capsule comprises HPMC (hydroxyl propyl methyl cellulose) or gelatin.

[0259] In some embodiments, the enteric coating comprises one enteric coating.

[0260] In some embodiments, the enteric coating comprises an inner enteric coating and an outer enteric coating, and wherein the inner and outer enteric coatings are not identical (e.g., the inner and outer enteric coatings do not contain identical components in identical amounts).

[0261] In some embodiments, the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) comprises a polymethacrylate-based copolymer.

[0262] In some embodiments, the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) comprises a methacrylic acid ethyl acrylate (MAE) copolymer (1:1).

[0263] In some embodiments, the one enteric coating comprises a methacrylic acid ethyl acrylate (MAE) copolymer (1:1) (such as Kollicoat MAE 100P).

[0264] In some embodiments, the one enteric coating comprises a Eudragit copolymer, e.g., a Eudragit L (e.g., Eudragit L 100-55; Eudragit L 30 D-55), a Eudragit S, a Eudragit RL, a Eudragit RS, a Eudragit E, or a Eudragit FS (e.g., Eudragit FS 30 D).

[0265] In some embodiments, the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) comprises cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), poly(vinyl acetate phthalate) (PVAP), hydroxypropyl methylcellulose phthalate (HPMCP), a fatty acid, a wax, shellac (esters of aleurtic acid), a plastic, a plant fiber, zein, Aqua-Zein (an aqueous zein formulation containing no alcohol), amylose starch, a starch derivative, a dextrin, a methyl acrylate-methacrylic acid copolymer, cellulose acetate succinate, hydroxypropyl methyl cellulose acetate succinate (hypromellose acetate succinate), a methyl methacrylate-methacrylic acid copolymer, or sodium alginate.

[0266] In some embodiments, the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) comprises an anionic polymeric material.

[0267] In some embodiments, the pharmaceutical agent comprises bacteria.

[0268] In some embodiments, the pharmaceutical agent comprises microbial extracellular vesicles (mEV).

[0269] In some embodiments, the pharmaceutical agent comprises bacteria and microbial extracellular vesicles (mEV).

[0270] In some embodiments, the pharmaceutical agent has one or more beneficial immune effects outside the gastrointestinal tract, e.g., when the solid dosage form is orally administered.

[0271] In some embodiments, the pharmaceutical agent modulates immune effects outside the gastrointestinal tract (e.g., outside of the small intestine) in the subject, e.g., when the solid dosage form is orally administered.

[0272] In some embodiments, the pharmaceutical agent causes a systemic effect (e.g., an effect outside of the gastrointestinal tract), e.g., when the solid dosage form is orally administered.

[0273] In some embodiments, the pharmaceutical agent acts on immune cells and/or epithelial cells in the small intestine (e.g., causing a systemic effect (e.g., an effect outside of the gastrointestinal tract)), e.g., when the solid dosage form is orally administered.

[0274] In some embodiments, the pharmaceutical agent comprises isolated bacteria (e.g., from one or more strains of bacteria (e.g., bacteria of interest) (e.g., a therapeutically effective amount thereof)). E.g., wherein at least 50%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% of the content of the pharmaceutical agent is the isolated bacteria (e.g., bacteria of interest).

[0275] In some embodiments, the pharmaceutical agent comprises bacteria that have been gamma irradiated, UV irradiated, heat inactivated, acid treated, or oxygen sparged.

[0276] In some embodiments, the pharmaceutical agent comprises live bacteria.

[0277] In some embodiments, the pharmaceutical agent comprises dead bacteria.

[0278] In some embodiments, the pharmaceutical agent comprises non-replicating bacteria.

- [0279] In some embodiments, the pharmaceutical agent comprises bacteria from one strain of microbe (e.g., bacteria).
- [0280] In some embodiments, the bacteria are lyophilized (e.g., the lyophilized product further comprises a pharmaceutically acceptable excipient) (e.g., a powder form).
- [0281] In some embodiments, the bacteria are gamma irradiated.
- [0282] In some embodiments, the bacteria are UV irradiated.
- [0283] In some embodiments, the bacteria are heat inactivated (e.g., at 50°C for two hours or at 90°C for two hours).
- [0284] In some embodiments, the bacteria are acid treated.
- [0285] In some embodiments, the bacteria are oxygen sparged (e.g., at 0.1 vvm for two hours).
- [0286] In some embodiments, the bacteria are Gram positive bacteria.
- [0287] In some embodiments, the bacteria are Gram negative bacteria.
- [0288] In some embodiments, the bacteria are aerobic bacteria.
- [0289] In some embodiments, the bacteria are anaerobic bacteria. In some embodiments, the anaerobic bacteria comprise obligate anaerobes. In some embodiments, the anaerobic bacteria comprise facultative anaerobes.
- [0290] In some embodiments, the bacteria are acidophile bacteria.
- [0291] In some embodiments, the bacteria are alkaliphile bacteria.
- [0292] In some embodiments, the bacteria are neutralophile bacteria.
- [0293] In some embodiments, the bacteria are fastidious bacteria.
- [0294] In some embodiments, the bacteria are nonfastidious bacteria.
- [0295] In some embodiments, the bacteria are of a taxonomic group (e.g., class, order, family, genus, species or strain) listed in Table 1, Table 2, or Table 3.
- [0296] In some embodiments, the bacteria are a bacterial strain listed in Table 1, Table 2, or Table 3.
- [0297] In some embodiments, the bacteria are of a taxonomic group (e.g., class, order, family, genus, species or strain) listed in Table J.
- [0298] In some embodiments, the bacteria are a bacterial strain listed in Table J.
- [0299] In some embodiments, the Gram negative bacteria belong to class *Negativicutes*.
- [0300] In some embodiments, the Gram negative bacteria belong to family *Veillonellaceae*, *Selenomonadaceae*, *Acidaminococcaceae*, or *Sporomusaceae*.

[0301] In some embodiments, the bacteria of the genus *Megasphaera*, *Selenomonas*, *Propionospora*, or *Acidaminococcus*.

[0302] In some embodiments, the bacteria are *Megasphaera* sp., *Selenomonas felix*, *Acidaminococcus intestine*, or *Propionospora* sp. bacteria.

[0303] In some embodiments, the bacteria are of the genus *Lactococcus*, *Prevotella*, *Bifidobacterium*, or *Veillonella*.

[0304] In some embodiments, the bacteria are *Lactococcus lactis cremoris* bacteria.

[0305] In some embodiments, the bacteria are *Prevotella histicola* bacteria.

[0306] In some embodiments, the bacteria are *Bifidobacterium animalis* bacteria.

[0307] In some embodiments, the bacteria are *Veillonella parvula* bacteria.

[0308] In some embodiments, the bacteria are *Lactococcus lactis cremoris* bacteria.

In some embodiments, the *Lactococcus lactis cremoris* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the *Lactococcus* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the *Lactococcus* bacteria are *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368).

[0309] In some embodiments, the bacteria are *Prevotella* bacteria. In some embodiments, the *Prevotella* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Prevotella* Strain B 50329 (NRRL accession number B 50329). In some embodiments, the *Prevotella* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Prevotella* Strain B 50329 (NRRL accession number B 50329). In some embodiments, the *Prevotella* bacteria are *Prevotella* Strain B 50329 (NRRL accession number B 50329).

[0310] In some embodiments, the bacteria are *Bifidobacterium* bacteria. In some embodiments, the *Bifidobacterium* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097. In some embodiments, the *Bifidobacterium* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium*

bacteria deposited as ATCC designation number PTA-125097. In some embodiments, the *Bifidobacterium* bacteria are *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097.

[0311] In some embodiments, the bacteria are *Veillonella* bacteria. In some embodiments, the *Veillonella* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the *Veillonella* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the *Veillonella* bacteria are *Veillonella* bacteria deposited as ATCC designation number PTA-125691.

[0312] In some embodiments, the bacteria are from *Ruminococcus gnavus* bacteria. In some embodiments, the *Ruminococcus gnavus* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695.

[0313] In some embodiments, the bacteria are *Megasphaera sp.* bacteria. In some embodiments, the *Megasphaera sp.* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some embodiments, the *Megasphaera sp.* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some embodiments, the *Megasphaera sp.* bacteria are *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770.

[0314] In some embodiments, the bacteria are *Fournierella massiliensis* bacteria. In some embodiments, the *Fournierella massiliensis* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide

sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696.

[0315] In some embodiments, the bacteria are *Harryflintia acetispora* bacteria. In some embodiments, the *Harryflintia acetispora* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694.

[0316] In some embodiments, the bacteria are of the family *Acidaminococcaceae*, *Alcaligenaceae*, *Akkermansiaceae*, *Bacteriodaceae*, *Bifidobacteriaceae*, *Burkholderiaceae*, *Catabacteriaceae*, *Clostridiaceae*, *Coriobacteriaceae*, *Enterobacteriaceae*, *Enterococcaceae*, *Fusobacteriaceae*, *Lachnospiraceae*, *Listeraceae*, *Mycobacteriaceae*, *Neisseriaceae*, *Odoribacteraceae*, *Oscillospiraceae*, *Peptococcaceae*, *Peptostreptococcaceae*, *Porphyromonadaceae*, *Prevotellaceae*, *Propionibacteraceae*, *Rikenellaceae*, *Ruminococcaceae*, *Selenomonadaceae*, *Sporomusaceae*, *Streptococcaceae*, *Streptomycetaceae*, *Sutterellaceae*, *Synergistaceae*, or *Veillonellaceae*.

[0317] In some embodiments, the bacteria are of the genus *Akkermansia*, *Christensenella*, *Blautia*, *Enterococcus*, *Eubacterium*, *Roseburia*, *Bacteroides*, *Parabacteroides*, or *Erysipelatoclostridium*.

[0318] In some embodiments, the bacteria are *Blautia hydrogenotrophica*, *Blautia stercoris*, *Blautia wexlerae*, *Eubacterium faecium*, *Eubacterium contortum*, *Eubacterium rectale*, *Enterococcus faecalis*, *Enterococcus durans*, *Enterococcus villorum*, *Enterococcus gallinarum*; *Bifidobacterium lactis*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, *Bifidobacterium animalis*, or *Bifidobacterium breve* bacteria.

[0319] In some embodiments, the bacteria are *BCG (bacillus Calmette-Guerin)*, *Parabacteroides*, *Blautia*, *Veillonella*, *Lactobacillus salivarius*, *Agathobaculum*,

Ruminococcus gnavus, *Paraclostridium benzoelyticum*, *Turicibacter sanguinus*, *Burkholderia*, *Klebsiella quasipneumoniae ssp similpneumoniae*, *Klebsiella oxytoca*, *Tyzzerelex nexilis*, or *Neisseria* bacteria.

- [0320] In some embodiments, the bacteria are *Blautia hydrogenotrophica* bacteria.
- [0321] In some embodiments, the bacteria are *Blautia stercoris* bacteria.
- [0322] In some embodiments, the bacteria are *Blautia wexlerae* bacteria.
- [0323] In some embodiments, the bacteria are *Enterococcus gallinarum* bacteria.
- [0324] In some embodiments, the bacteria are *Enterococcus faecium* bacteria.
- [0325] In some embodiments, the bacteria are *Bifidobacterium bifidum* bacteria.
- [0326] In some embodiments, the bacteria are *Bifidobacterium breve* bacteria.
- [0327] In some embodiments, the bacteria are *Bifidobacterium longum* bacteria.
- [0328] In some embodiments, the bacteria are *Roseburia hominis* bacteria.
- [0329] In some embodiments, the bacteria are *Bacteroides thetaiotaomicron* bacteria.
- [0330] In some embodiments, the bacteria are *Bacteroides coprocola* bacteria.
- [0331] In some embodiments, the bacteria are *Erysipelatoclostridium ramosum* bacteria.
- [0332] In some embodiments, the bacteria are *Megasphaera massiliensis* bacteria.
- [0333] In some embodiments, the bacteria are *Eubacterium* bacteria.
- [0334] In some embodiments, the bacteria are *Parabacteroides distasonis* bacteria.
- [0335] In some embodiments, the bacteria are *Lactobacillus plantarum* bacteria.
- [0336] In some embodiments, the bacteria are bacteria of the *Negativicutes* class.
- [0337] In some embodiments, the bacteria are of the *Veillonellaceae* family.
- [0338] In some embodiments, the bacteria are of the *Selenomonadaceae* family.
- [0339] In some embodiments, the bacteria are of the *Acidaminococcaceae* family.
- [0340] In some embodiments, the bacteria are of the *Sporomusaceae* family.
- [0341] In some embodiments, the bacteria are of the *Megasphaera* genus.
- [0342] In some embodiments, the bacteria are of the *Selenomonas* genus.
- [0343] In some embodiments, the bacteria are of the *Propionospora* genus.
- [0344] In some embodiments, the bacteria are of the *Acidaminococcus* genus.
- [0345] In some embodiments, the bacteria are *Megasphaera sp.* bacteria.
- [0346] In some embodiments, the bacteria are *Selenomonas felix* bacteria.
- [0347] In some embodiments, the bacteria are *Acidaminococcus intestini* bacteria.

- [0348] In some embodiments, the bacteria are *Propionospora sp.* bacteria.
- [0349] In some embodiments, the bacteria are bacteria of the *Clostridia* class.
- [0350] In some embodiments, the bacteria are of the *Oscillospiraceae* family.
- [0351] In some embodiments, the bacteria are of the *Faecalibacterium* genus.
- [0352] In some embodiments, the bacteria are of the *Fournierella* genus.
- [0353] In some embodiments, the bacteria are of the *Harryflintia* genus.
- [0354] In some embodiments, the bacteria are of the *Agathobaculum* genus.
- [0355] In some embodiments, the bacteria are *Faecalibacterium prausnitzii* (e.g., *Faecalibacterium prausnitzii* Strain A) bacteria.
- [0356] In some embodiments, the bacteria are *Fournierella massiliensis* (e.g., *Fournierella massiliensis* Strain A) bacteria.
- [0357] In some embodiments, the bacteria are *Harryflintia acetispora* (e.g., *Harryflintia acetispora* Strain A) bacteria.
- [0358] In some embodiments, the bacteria are *Agathobaculum sp.* (e.g., *Agathobaculum sp.* Strain A) bacteria.
- [0359] In some embodiments, the bacteria are a strain of *Agathobaculum sp.* In some embodiments, the *Agathobaculum sp.* strain is a strain comprising at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity (e.g., at least 99.5% sequence identity, at least 99.6% sequence identity, at least 99.7% sequence identity, at least 99.8% sequence identity, at least 99.9% sequence identity) to the nucleotide sequence (e.g., genomic sequence, 16S sequence, CRISPR sequence) of the *Agathobaculum sp.* Strain A (ATCC Deposit Number PTA-125892). In some embodiments, the *Agathobaculum sp.* strain is the *Agathobaculum sp.* Strain A (ATCC Deposit Number PTA-125892).
- [0360] In some embodiments, the bacteria are of the class *Bacteroidia* [phylum *Bacteroidota*]. In some embodiments, the bacteria are of order *Bacteroidales*. In some embodiments, the bacteria are of the family *Porphyromonadaceae*. In some embodiments, the bacteria are of the family *Prevotellaceae*. In some embodiments, the bacteria are of the class *Bacteroidia* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the bacteria are of the class *Bacteroidia* that stain Gram negative. In some embodiments, the bacteria are of the class *Bacteroidia* wherein the bacteria is diderm and the bacteria stain Gram negative.

[0361] In some embodiments, the bacteria are of the class *Clostridia* [phylum *Firmicutes*]. In some embodiments, the bacteria are of the order *Eubacteriales*. In some embodiments, the bacteria are of the family *Oscillispiraceae*. In some embodiments, the bacteria are of the family *Lachnospiraceae*. In some embodiments, the bacteria are of the family *Peptostreptococcaceae*. In some embodiments, the bacteria are of the family *Clostridiales* family XIII/ *Incertae sedis* 41. In some embodiments, the bacteria are of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm. In some embodiments, the bacteria are of the class *Clostridia* that stain Gram negative. In some embodiments, the bacteria are of the class *Clostridia* that stain Gram positive. In some embodiments, the bacteria are of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram negative. In some embodiments, the bacteria are of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram positive.

[0362] In some embodiments, the bacteria are of the class *Negativicutes* [phylum *Firmicutes*]. In some embodiments, the bacteria are of the order *Veillonellales*. In some embodiments, the bacteria are of the family *Veillonelloceae*. In some embodiments, the bacteria are of the order *Selenomonadales*. In some embodiments, the bacteria are of the family *Selenomonadaceae*. In some embodiments, the bacteria are of the family *Sporomusaceae*. In some embodiments, the bacteria are of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the bacteria are of the class *Negativicutes* that stain Gram negative. In some embodiments, the bacteria are of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[0363] In some embodiments, the bacteria are of the class *Synergistia* [phylum *Synergistota*]. In some embodiments, the bacteria are of the order *Synergistales*. In some embodiments, the bacteria are of the family *Synergistaceae*. In some embodiments, the bacteria are of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the bacteria are of the class *Synergistia* that stain Gram negative. In some embodiments, the bacteria are of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[0364] In some embodiments, the bacteria are bacteria that produce metabolites, e.g., the bacteria produce butyrate, ioline, propionate, or tryptophan metabolites.

[0365] In some embodiments, the bacteria produce butyrate. In some embodiments, the bacteria are from the genus *Blautia*; *Christensenella*; *Copracoccus*; *Eubacterium*; *Lachnospiraceae*; *Megasphaera*; or *Roseburia*.

[0366] In some embodiments, the bacteria produce isosine. In some embodiments, the bacteria are from the genus *Bifidobacterium*; *Lactobacillus*; or *Olsenella*.

[0367] In some embodiments, the bacteria produce propionate. In some embodiments, the bacteria are from the genus *Akkermansia*; *Bacteriodes*; *Dialister*; *Eubacterium*; *Megasphaera*; *Parabacteriodes*; *Prevotella*; *Ruminococcus*; or *Veillonella*.

[0368] In some embodiments, the bacteria produce tryptophan metabolites. In some embodiments, the bacteria are from the genus *Lactobacillus* or *Peptostreptococcus*.

[0369] In some embodiments, the bacteria are bacteria that produce inhibitors of histone deacetylase 3 (HDAC3). In some embodiments, the bacteria are from the species *Bariatricus massiliensis*, *Faecalibacterium prausnitzii*, *Megasphaera massiliensis* or *Roseburia intestinalis*.

[0370] In some embodiments, the pharmaceutical agent comprises isolated mEVs (e.g., from one or more strains of bacteria (e.g., bacteria of interest)) (e.g., a therapeutically effective amount thereof). E.g., wherein at least 50%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% of the content of the pharmaceutical agent is isolated mEV of bacteria (e.g., bacteria of interest).

[0371] In some embodiments, the pharmaceutical agent comprises mEVs and the mEVs comprise secreted mEVs (smEVs).

[0372] In some embodiments, the pharmaceutical agent comprises mEVs and the mEVs comprise processed mEVs (pmEVs).

[0373] In some embodiments, the pharmaceutical agent comprises pmEVs and the pmEVs are produced from bacteria that have been gamma irradiated, UV irradiated, heat inactivated, acid treated, or oxygen sparged.

[0374] In some embodiments, the pharmaceutical agent comprises pmEVs and the pmEVs are produced from live bacteria.

[0375] In some embodiments, the pharmaceutical agent comprises pmEVs and the pmEVs are produced from dead bacteria.

[0376] In some embodiments, the pharmaceutical agent comprises pmEVs and the pmEVs are produced from non-replicating bacteria.

- [0377] In some embodiments, the pharmaceutical agent comprises mEVs and the mEVs are from one strain of bacteria.
- [0378] In some embodiments, the mEVs are lyophilized (e.g., the lyophilized product further comprises a pharmaceutically acceptable excipient).
- [0379] In some embodiments, the mEVs are gamma irradiated.
- [0380] In some embodiments, the mEVs are UV irradiated.
- [0381] In some embodiments, the mEVs are heat inactivated (e.g., at 50°C for two hours or at 90°C for two hours).
- [0382] In some embodiments, the mEVs are acid treated.
- [0383] In some embodiments, the mEVs are oxygen sparged (e.g., at 0.1 vvm for two hours).
- [0384] In some embodiments, the mEVs are from Gram positive bacteria.
- [0385] In some embodiments, the mEVs are from Gram negative bacteria.
- [0386] In some embodiments, the mEVs are from aerobic bacteria.
- [0387] In some embodiments, the mEVs are from anaerobic bacteria. In some embodiments, the anaerobic bacteria comprise obligate anaerobes. In some embodiments, the anaerobic bacteria comprise facultative anaerobes.
- [0388] In some embodiments, the mEVs are from acidophile bacteria.
- [0389] In some embodiments, the mEVs are from alkaliphile bacteria.
- [0390] In some embodiments, the mEVs are from neutralophile bacteria.
- [0391] In some embodiments, the mEVs are from fastidious bacteria.
- [0392] In some embodiments, the mEVs are from nonfastidious bacteria.
- [0393] In some embodiments, the mEVs are from bacteria of a taxonomic group (e.g., class, order, family, genus, species or strain) listed in Table 1, Table 2, or Table 3.
- [0394] In some embodiments, the mEVs are from a bacterial strain listed in Table 1, Table 2, or Table 3.
- [0395] In some embodiments, the mEVs are from bacteria of a taxonomic group (e.g., class, order, family, genus, species or strain) listed in Table J.
- [0396] In some embodiments, the mEVs are from a bacterial strain listed in Table J.
- [0397] In some embodiments, the Gram negative bacteria belong to class *Negativicutes*.
- [0398] In some embodiments, the Gram negative bacteria belong to family *Veillonellaceae*, *Selenomonadaceae*, *Acidaminococcaceae*, or *Sporomusaceae*.

- [0399] In some embodiments, the mEVs are from bacteria of the genus *Megasphaera*, *Selenomonas*, *Propionospora*, or *Acidaminococcus*.
- [0400] In some embodiments, the mEVs are *Megasphaera sp.*, *Selenomonas felix*, *Acidaminococcus intestine*, or *Propionospora sp.* bacteria.
- [0401] In some embodiments, the mEVs are from bacteria of the genus *Lactococcus*, *Prevotella*, *Bifidobacterium*, or *Veillonella*.
- [0402] In some embodiments, the mEVs are from *Lactococcus lactis cremoris* bacteria.
- [0403] In some embodiments, the mEVs are from *Prevotella histicola* bacteria.
- [0404] In some embodiments, the mEVs are from *Bifidobacterium animalis* bacteria.
- [0405] In some embodiments, the mEVs are from *Veillonella parvula* bacteria.
- [0406] In some embodiments, the mEVs are from *Lactococcus lactis cremoris* bacteria. In some embodiments, the *Lactococcus lactis cremoris* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the *Lactococcus* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the *Lactococcus* bacteria are from *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368).
- [0407] In some embodiments, the mEVs are from *Prevotella* bacteria. In some embodiments, the *Prevotella* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Prevotella* Strain B 50329 (NRRL accession number B 50329). In some embodiments, the *Prevotella* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Prevotella* Strain B 50329 (NRRL accession number B 50329). In some embodiments, the *Prevotella* bacteria are from *Prevotella* Strain B 50329 (NRRL accession number B 50329).
- [0408] In some embodiments, the mEVs are from *Bifidobacterium* bacteria. In some embodiments, the *Bifidobacterium* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097. In some

embodiments, the *Bifidobacterium* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097. In some embodiments, the *Bifidobacterium* bacteria are from *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097.

[0409] In some embodiments, the mEVs are from *Veillonella* bacteria. In some embodiments, the *Veillonella* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the *Veillonella* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the *Veillonella* bacteria are from *Veillonella* bacteria deposited as ATCC designation number PTA-125691.

[0410] In some embodiments, the mEVs are from *Ruminococcus gnavus* bacteria. In some embodiments, the *Ruminococcus gnavus* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are from *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695.

[0411] In some embodiments, the mEVs are from *Megasphaera sp.* bacteria. In some embodiments, the *Megasphaera sp.* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some embodiments, the *Megasphaera sp.* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some embodiments, the *Megasphaera sp.* bacteria are from *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770.

[0412] In some embodiments, the mEVs are from *Fournierella massiliensis* bacteria. In some embodiments, the *Fournierella massiliensis* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are from *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696.

[0413] In some embodiments, the mEVs are from *Harryflintia acetispora* bacteria. In some embodiments, the *Harryflintia acetispora* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are from *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694.

[0414] In some embodiments, the mEVs are from bacteria of the family *Acidaminococcaceae*, *Alcaligenaceae*, *Akkermansiaceae*, *Bacteriodaceae*, *Bifidobacteriaceae*, *Burkholderiaceae*, *Catabacteriaceae*, *Clostridiaceae*, *Coriobacteriaceae*, *Enterobacteriaceae*, *Enterococcaceae*, *Fusobacteriaceae*, *Lachnospiraceae*, *Listeraceae*, *Mycobacteriaceae*, *Neisseriaceae*, *Odoribacteraceae*, *Oscillospiraceae*, *Peptococcaceae*, *Peptostreptococcaceae*, *Porphyromonadaceae*, *Prevotellaceae*, *Propionibacteraceae*, *Rikenellaceae*, *Ruminococcaceae*, *Selenomonadaceae*, *Sporomusaceae*, *Streptococcaceae*, *Streptomyetaceae*, *Sutterellaceae*, *Synergistaceae*, or *Veillonellaceae*.

[0415] In some embodiments, the mEVs are from bacteria of the genus *Akkermansia*, *Christensenella*, *Blautia*, *Enterococcus*, *Eubacterium*, *Roseburia*, *Bacteroides*, *Parabacteroides*, or *Erysipelatoclostridium*.

[0416] In some embodiments, the mEVs are from *Blautia hydrogenotrophica*, *Blautia stercoris*, *Blautia wexlerae*, *Eubacterium faecium*, *Eubacterium contortum*,

Eubacterium rectale, *Enterococcus faecalis*, *Enterococcus durans*, *Enterococcus villorum*, *Enterococcus gallinarum*; *Bifidobacterium lactis*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, *Bifidobacterium animalis*, or *Bifidobacterium breve* bacteria.

[0417] In some embodiments, the mEVs are from *BCG (bacillus Calmette-Guerin)*, *Parabacteroides*, *Blautia*, *Veillonella*, *Lactobacillus salivarius*, *Agathobaculum*, *Ruminococcus gnavus*, *Paraclostridium benzoelyticum*, *Turicibacter sanguinus*, *Burkholderia*, *Klebsiella quasipneumoniae ssp simipneumoniae*, *Klebsiella oxytoca*, *Tyzzerelex nexilis*, or *Neisseria* bacteria.

[0418] In some embodiments, the mEVs are from *Blautia hydrogenotrophica* bacteria.

[0419] In some embodiments, the mEVs are from *Blautia stercoris* bacteria.

[0420] In some embodiments, the mEVs are from *Blautia wexlerae* bacteria.

[0421] In some embodiments, the mEVs are from *Enterococcus gallinarum* bacteria.

[0422] In some embodiments, the mEVs are from *Enterococcus faecium* bacteria.

[0423] In some embodiments, the mEVs are from *Bifidobacterium bifidum* bacteria.

[0424] In some embodiments, the mEVs are from *Bifidobacterium breve* bacteria.

[0425] In some embodiments, the mEVs are from *Bifidobacterium longum* bacteria.

[0426] In some embodiments, the mEVs are from *Roseburia hominis* bacteria.

[0427] In some embodiments, the mEVs are from *Bacteroides thetaiotaomicron* bacteria.

[0428] In some embodiments, the mEVs are from *Bacteroides coprocola* bacteria.

[0429] In some embodiments, the mEVs are from *Erysipelatoclostridium ramosum* bacteria.

[0430] In some embodiments, the mEVs are from *Megasphera massiliensis* bacteria.

[0431] In some embodiments, the mEVs are from *Eubacterium* bacteria.

[0432] In some embodiments, the mEVs are from *Parabacteroides distasonis* bacteria.

[0433] In some embodiments, the mEVs are from *Lactobacillus plantarum* bacteria.

[0434] In some embodiments, the mEVs are from bacteria of the *Negativicutes* class.

- [0435] In some embodiments, the mEVs are from bacteria of the *Veillonellaceae* family.
- [0436] In some embodiments, the mEVs are from bacteria of the *Selenomonadaceae* family.
- [0437] In some embodiments, the mEVs are from bacteria of the *Acidaminococcaceae* family.
- [0438] In some embodiments, the mEVs are from bacteria of the *Sporomusaceae* family.
- [0439] In some embodiments, the mEVs are from bacteria of the *Megasphaera* genus.
- [0440] In some embodiments, the mEVs are from bacteria of the *Selenomonas* genus.
- [0441] In some embodiments, the mEVs are from bacteria of the *Propionospora* genus.
- [0442] In some embodiments, the mEVs are from bacteria of the *Acidaminococcus* genus.
- [0443] In some embodiments, the mEVs are from *Megasphaera sp.* bacteria.
- [0444] In some embodiments, the mEVs are from *Selenomonas felix* bacteria.
- [0445] In some embodiments, the mEVs are from *Acidaminococcus intestini* bacteria.
- [0446] In some embodiments, the mEVs are from *Propionospora sp.* bacteria.
- [0447] In some embodiments, the mEVs are from bacteria of the *Clostridia* class.
- [0448] In some embodiments, the mEVs are from bacteria of the *Oscillospiraceae* family.
- [0449] In some embodiments, the mEVs are from bacteria of the *Faecalibacterium* genus.
- [0450] In some embodiments, the mEVs are from bacteria of the *Fournierella* genus.
- [0451] In some embodiments, the mEVs are from bacteria of the *Harryflintia* genus.
- [0452] In some embodiments, the mEVs are from bacteria of the *Agathobaculum* genus.
- [0453] In some embodiments, the mEVs are from *Faecalibacterium prausnitzii* (e.g., *Faecalibacterium prausnitzii* Strain A) bacteria.

[0454] In some embodiments, the mEVs are from *Fournierella massiliensis* (e.g., *Fournierella massiliensis* Strain A) bacteria.

[0455] In some embodiments, the mEVs are from *Harryflintia acetispora* (e.g., *Harryflintia acetispora* Strain A) bacteria.

[0456] In some embodiments, the mEVs are from *Agathobaculum sp.* (e.g., *Agathobaculum sp.* Strain A) bacteria.

[0457] In some embodiments, the mEVs are from a strain of *Agathobaculum sp.* In some embodiments, the *Agathobaculum sp.* strain is a strain comprising at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity (e.g., at least 99.5% sequence identity, at least 99.6% sequence identity, at least 99.7% sequence identity, at least 99.8% sequence identity, at least 99.9% sequence identity) to the nucleotide sequence (e.g., genomic sequence, 16S sequence, CRISPR sequence) of the *Agathobaculum sp.* Strain A (ATCC Deposit Number PTA-125892). In some embodiments, the *Agathobaculum sp.* strain is the *Agathobaculum sp.* Strain A (ATCC Deposit Number PTA-125892).

[0458] In some embodiments, the mEVs are from bacteria of the class *Bacteroidia* [phylum *Bacteroidota*]. In some embodiments, the mEVs are from bacteria of order *Bacteroidales*. In some embodiments, the mEVs are from bacteria of the family *Porphyromonadaceae*. In some embodiments, the mEVs are from bacteria of the family *Prevotellaceae*. In some embodiments, the mEVs are from bacteria of the class *Bacteroidia* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the mEVs are from bacteria of the class *Bacteroidia* that stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Bacteroidia* wherein the bacteria is diderm and the bacteria stain Gram negative.

[0459] In some embodiments, the mEVs are from bacteria of the class *Clostridia* [phylum *Firmicutes*]. In some embodiments, the mEVs are from bacteria of the order *Eubacteriales*. In some embodiments, the mEVs are from bacteria of the family *Oscillispiraceae*. In some embodiments, the mEVs are from bacteria of the family *Lachnospiraceae*. In some embodiments, the mEVs are from bacteria of the family *Peptostreptococcaceae*. In some embodiments, the mEVs are from bacteria of the family *Clostridiales family XIII/ Incertae sedis 41*. In some embodiments, the mEVs are from bacteria of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm. In some embodiments, the mEVs are from bacteria of the class *Clostridia* that

stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Clostridia* that stain Gram positive. In some embodiments, the mEVs are from bacteria of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram positive.

[0460] In some embodiments, the mEVs are from bacteria of the class *Negativicutes* [phylum *Firmicutes*]. In some embodiments, the mEVs are from bacteria of the order *Veillonellales*. In some embodiments, the mEVs are from bacteria of the family *Veillonelloceae*. In some embodiments, the mEVs are from bacteria of the order *Selenomonadales*. In some embodiments, the mEVs are from bacteria of the family *Selenomonadaceae*. In some embodiments, the mEVs are from bacteria of the family *Sporomusaceae*. In some embodiments, the mEVs are from bacteria of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the mEVs are from bacteria of the class *Negativicutes* that stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[0461] In some embodiments, the mEVs are from bacteria of the class *Synergistia* [phylum *Synergistota*]. In some embodiments, the mEVs are from bacteria of the order *Synergistales*. In some embodiments, the mEVs are from bacteria of the family *Synergistaceae*. In some embodiments, the mEVs are from bacteria of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the mEVs are from bacteria of the class *Synergistia* that stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[0462] In some embodiments, the mEVs are from bacteria that produce metabolites, e.g., the bacteria produce butyrate, iosine, proprionate, or tryptophan metabolites.

[0463] In some embodiments, the bacteria produce butyrate. In some embodiments, the bacteria are from the genus *Blautia*; *Christensella*; *Copracoccus*; *Eubacterium*; *Lachnosperacea*; *Megasphaera*; or *Roseburia*.

[0464] In some embodiments, the bacteria produce iosine. In some embodiments, the bacteria are from the genus *Bifidobacterium*; *Lactobacillus*; or *Olsenella*.

[0465] In some embodiments, the bacteria produce propionate. In some embodiments, the bacteria are from the genus *Akkermansia*; *Bacteriodes*; *Dialister*; *Eubacterium*; *Megasphaera*; *Parabacteriodes*; *Prevotella*; *Ruminococcus*; or *Veillonella*.

[0466] In some embodiments, the bacteria produce tryptophan metabolites. In some embodiments, the bacteria are from the genus *Lactobacillus* or *Peptostreptococcus*.

[0467] In some embodiments, the mEVs are from bacteria that produce inhibitors of histone deacetylase 3 (HDAC3). In some embodiments, the bacteria are from the species *Bariatricus massiliensis*, *Faecalibacterium prausnitzii*, *Megasphaera massiliensis* or *Roseburia intestinalis*.

[0468] In some embodiments, the pharmaceutical agent comprises bacteria and the dose of bacteria is about 1×10^7 to about 2×10^{12} (e.g., about 3×10^{10} or about 1.5×10^{11} or about 1.5×10^{12}) cells (e.g., wherein cell number is determined by total cell count, which is determined by Coulter counter), wherein the dose is per capsule or tablet or per total number of minitables in a capsule. In some embodiments, the pharmaceutical agent comprises bacteria and the dose of bacteria is about 1×10^{10} to about 2×10^{12} (e.g., about 1.6×10^{11} or about 8×10^{11} or about 9.6×10^{11} or about 12.8×10^{11} or about 1.6×10^{12}) cells (e.g., wherein cell number is determined by total cell count, which is determined by Coulter counter), wherein the dose is per capsule or tablet or per total number of minitables in a capsule.

[0469] In some embodiments, the pharmaceutical agent comprises bacteria and the dose of bacteria is about 1×10^9 , about 3×10^9 , about 5×10^9 , about 1.5×10^{10} , about 3×10^{10} , about 5×10^{10} , about 1.5×10^{11} , about 1.5×10^{12} , or about 2×10^{12} cells, wherein the dose is per capsule or tablet or per total number of minitables in a capsule.

[0470] In some embodiments, the pharmaceutical agent comprises mEVs and the dose of mEVs is about 1×10^5 to about 7×10^{13} particles (e.g., wherein particle count is determined by NTA (nanoparticle tracking analysis)), wherein the dose is per capsule or tablet or per total number of minitables in a capsule. In some embodiments, the pharmaceutical agent comprises mEVs and the dose of mEVs is about 1×10^{10} to about 7×10^{13} particles (e.g., wherein particle count is determined by NTA (nanoparticle tracking analysis)), wherein the dose is per capsule or tablet or per total number of minitables in a capsule.

[0471] In some embodiments, the pharmaceutical agent comprises bacteria and/or mEVs and the dose of drug substance that contains the pharmaceutical agent (e.g., bacteria

and/or mEVs) is about 10 mg to about 3500 mg, wherein the dose is per capsule or tablet or per total number of minitabets in a capsule.

[0472] In some embodiments, the pharmaceutical agent comprises bacteria and/or mEVs and the dose of drug substance that contains the pharmaceutical agent (e.g., bacteria and/or mEVs) is about 30 mg to about 1300 mg (by weight of bacteria and/or mEVs) (about 25, about 30, about 35, about 50, about 75, about 100, about 120, about 150, about 250, about 300, about 350, about 400, about 500, about 600, about 700, about 750, about 800, about 900, about 1000, about 1100, about 1200, about 1250, about 1300, about 2000, about 2500, about 3000, or about 3500 mg, wherein the dose is per capsule or tablet or per total number of minitabets in a capsule.

[0473] In some embodiments, the pharmaceutical agent comprises bacteria and/or mEVs and the dose of pharmaceutical agent (e.g., bacteria and/or mEVs) is about 2×10^6 to about 2×10^{16} particles (e.g., wherein particle count is determined by NTA (nanoparticle tracking analysis)), wherein the dose is per capsule or tablet or per total number of minitabets in a capsule.

[0474] In some embodiments, the pharmaceutical agent comprises bacteria and/or mEVs and the dose of the pharmaceutical agent (e.g., bacteria and/or mEVs) is about 5 mg to about 900 mg total protein (e.g., wherein total protein is determined by Bradford assay or BCA), wherein the dose is per capsule or tablet or per total number of minitabets in a capsule.

[0475] In some embodiments, the solid dosage form further comprises one or more additional pharmaceutical agents.

[0476] In some embodiments, the solid dosage form further comprises an excipient (e.g., an excipient described herein, e.g., a diluent, a binder and/or an adhesive, a disintegrant, a lubricant and/or a glidant, a coloring agent, a flavoring agent, and/or a sweetening agent).

[0477] In some aspects, the disclosure provides a method for preparing an enterically coated capsule comprising a pharmaceutical agent (e.g., a therapeutically effective amount thereof), wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), the method comprising:

[0478] a) loading the pharmaceutical agent into a capsule; and

[0479] b) enterically coating the capsule, thereby preparing the enterically coated capsule.

[0480] In some embodiments, the method comprises combining the pharmaceutical agent with a pharmaceutically acceptable excipient prior to loading into the capsule.

[0481] In some embodiments, the method for preparing an enterically coated capsule comprising a pharmaceutical agent (e.g., a therapeutically effective amount thereof), wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), comprises:

[0482] a) combining the pharmaceutical agent with a pharmaceutically acceptable excipient;

[0483] b) loading the pharmaceutical agent and pharmaceutically acceptable excipient into a capsule; and

[0484] c) enterically coating the capsule, thereby preparing the enterically coated capsule.

[0485] In some embodiments, the method further comprises banding the capsule after loading the capsule and prior to enterically coating the capsule. In some embodiments, the capsule is banded with an HPMC-based banding solution.

[0486] In some embodiments, the disclosure provides a method for preparing an enterically coated capsule comprising a pharmaceutical agent (e.g., a therapeutically effective amount thereof), wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), the method comprising:

[0487] a) loading the pharmaceutical agent into a capsule;

[0488] b) banding the capsule; and

[0489] c) enterically coating the capsule, thereby preparing the enterically coated capsule.

[0490] In some embodiments, the disclosure provides a method for preparing an enterically coated capsule comprising a pharmaceutical agent (e.g., a therapeutically effective amount thereof), wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), the method comprising:

[0491] a) combining the pharmaceutical agent with a pharmaceutically acceptable excipient;

[0492] b) loading the pharmaceutical agent and pharmaceutically acceptable excipient into a capsule;

[0493] c) banding the capsule; and

[0494] d) enterically coating the capsule, thereby preparing the enterically coated capsule.

[0495] In certain embodiments, the solid dosage form comprises a capsule. In some embodiments, the capsule is a size 00, size 0, size 1, size 2, size 3, size 4, or size 5 capsule. In some embodiments, the capsule is a size 0 capsule.

[0496] In some embodiments, the capsule comprises HPMC or gelatin. In some embodiments, the capsule comprises HPMC.

[0497] In some embodiments, the enteric coating comprises an inner enteric coating and an outer enteric coating, and wherein the inner and outer enteric coatings are not identical (e.g., the inner and outer enteric coatings do not contain identical components in identical amounts).

[0498] In some embodiments, the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) comprises a polymethacrylate-based copolymer.

[0499] In some embodiments, the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) comprises a methacrylic acid ethyl acrylate (MAE) copolymer (1:1).

[0500] In some embodiments, the one enteric coating comprises a methacrylic acid ethyl acrylate (MAE) copolymer (1:1) (such as Kollicoat MAE 100P).

[0501] In some embodiments, the one enteric coating comprises a Eudragit copolymer, e.g., a Eudragit L (e.g., Eudragit L 100-55; Eudragit L 30 D-55), a Eudragit S, a Eudragit RL, a Eudragit RS, a Eudragit E, or a Eudragit FS (e.g., Eudragit FS 30 D).

[0502] In some embodiments, the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) comprises cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), poly(vinyl acetate phthalate) (PVAP), hydroxypropyl methylcellulose phthalate (HPMCP), a fatty acid, a wax, shellac (esters of aleuritic acid), a plastic, a plant fiber, zein, Aqua-Zein (an aqueous zein formulation containing no alcohol), amylose starch, a starch derivative, a dextrin, a methyl acrylate-methacrylic acid copolymer, cellulose acetate succinate, hydroxypropyl methyl cellulose acetate succinate (hypromellose acetate succinate), a methyl methacrylate-methacrylic acid copolymer, or sodium alginate.

- [0503] In some embodiments, the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) comprises an anionic polymeric material.
- [0504] In some embodiments, the pharmaceutical agent comprises bacteria.
- [0505] In some embodiments, the pharmaceutical agent comprises microbial extracellular vesicles (mEV).
- [0506] In some embodiments, the pharmaceutical agent comprises bacteria and microbial extracellular vesicles (mEV).
- [0507] In some embodiments, the pharmaceutical agent has one or more beneficial immune effects outside the gastrointestinal tract, e.g., when the solid dosage form is orally administered.
- [0508] In some embodiments, the pharmaceutical agent modulates immune effects outside the gastrointestinal tract (e.g., outside of the small intestine) in the subject, e.g., when the solid dosage form is orally administered.
- [0509] In some embodiments, the pharmaceutical agent causes a systemic effect (e.g., an effect outside of the gastrointestinal tract), e.g., when the solid dosage form is orally administered.
- [0510] In some embodiments, the pharmaceutical agent acts on immune cells and/or epithelial cells in the small intestine (e.g., causing a systemic effect (e.g., an effect outside of the gastrointestinal tract), e.g., when the solid dosage form is orally administered.
- [0511] In some embodiments, the pharmaceutical agent comprises isolated bacteria (e.g., from one or more strains of bacteria (e.g., bacteria of interest) (e.g., a therapeutically effective amount thereof)). E.g., wherein at least 50%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% of the content of the pharmaceutical agent is the isolated bacteria (e.g., bacteria of interest).
- [0512] In some embodiments, the pharmaceutical agent comprises bacteria that have been gamma irradiated, UV irradiated, heat inactivated, acid treated, or oxygen sparged.
- [0513] In some embodiments, the pharmaceutical agent comprises live bacteria.
- [0514] In some embodiments, the pharmaceutical agent comprises dead bacteria.
- [0515] In some embodiments, the pharmaceutical agent comprises non-replicating bacteria.

- [0516] In some embodiments, the pharmaceutical agent comprises bacteria from one strain of microbe (e.g., bacteria).
- [0517] In some embodiments, the bacteria are lyophilized (e.g., the lyophilized product further comprises a pharmaceutically acceptable excipient) (e.g., a powder form).
- [0518] In some embodiments, the bacteria are gamma irradiated.
- [0519] In some embodiments, the bacteria are UV irradiated.
- [0520] In some embodiments, the bacteria are heat inactivated (e.g., at 50°C for two hours or at 90°C for two hours).
- [0521] In some embodiments, the bacteria are acid treated.
- [0522] In some embodiments, the bacteria are oxygen sparged (e.g., at 0.1 vvm for two hours).
- [0523] In some embodiments, the bacteria are Gram positive bacteria.
- [0524] In some embodiments, the bacteria are Gram negative bacteria.
- [0525] In some embodiments, the bacteria are aerobic bacteria.
- [0526] In some embodiments, the bacteria are anaerobic bacteria. In some embodiments, the anaerobic bacteria comprise obligate anaerobes. In some embodiments, the anaerobic bacteria comprise facultative anaerobes.
- [0527] In some embodiments, the bacteria are acidophile bacteria.
- [0528] In some embodiments, the bacteria are alkaliphile bacteria.
- [0529] In some embodiments, the bacteria are neutralophile bacteria.
- [0530] In some embodiments, the bacteria are fastidious bacteria.
- [0531] In some embodiments, the bacteria are nonfastidious bacteria.
- [0532] In some embodiments, the bacteria are of a taxonomic group (e.g., class, order, family, genus, species or strain) listed in Table 1, Table 2, or Table 3.
- [0533] In some embodiments, the bacteria are a bacterial strain listed in Table 1, Table 2, or Table 3.
- [0534] In some embodiments, the bacteria are of a taxonomic group (e.g., class, order, family, genus, species or strain) listed in Table J.
- [0535] In some embodiments, the bacteria are a bacterial strain listed in Table J.
- [0536] In some embodiments, the Gram negative bacteria belong to class *Negativicutes*.
- [0537] In some embodiments, the Gram negative bacteria belong to family *Veillonellaceae*, *Selenomonadaceae*, *Acidaminococcaceae*, or *Sporomusaceae*.

[0538] In some embodiments, the bacteria of the genus *Megasphaera*, *Selenomonas*, *Propionospora*, or *Acidaminococcus*.

[0539] In some embodiments, the bacteria are *Megasphaera* sp., *Selenomonas felix*, *Acidaminococcus intestine*, or *Propionospora* sp. bacteria.

[0540] In some embodiments, the bacteria are of the genus *Lactococcus*, *Prevotella*, *Bifidobacterium*, or *Veillonella*.

[0541] In some embodiments, the bacteria are *Lactococcus lactis cremoris* bacteria.

[0542] In some embodiments, the bacteria are *Prevotella histicola* bacteria.

[0543] In some embodiments, the bacteria are *Bifidobacterium animalis* bacteria.

[0544] In some embodiments, the bacteria are *Veillonella parvula* bacteria.

[0545] In some embodiments, the bacteria are *Lactococcus lactis cremoris* bacteria.

In some embodiments, the *Lactococcus lactis cremoris* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the *Lactococcus* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the *Lactococcus* bacteria are *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368).

[0546] In some embodiments, the bacteria are *Prevotella* bacteria. In some embodiments, the *Prevotella* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Prevotella* Strain B 50329 (NRRL accession number B 50329). In some embodiments, the *Prevotella* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Prevotella* Strain B 50329 (NRRL accession number B 50329). In some embodiments, the *Prevotella* bacteria are *Prevotella* Strain B 50329 (NRRL accession number B 50329).

[0547] In some embodiments, the bacteria are *Bifidobacterium* bacteria. In some embodiments, the *Bifidobacterium* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097. In some embodiments, the *Bifidobacterium* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium*

bacteria deposited as ATCC designation number PTA-125097. In some embodiments, the *Bifidobacterium* bacteria are *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097.

[0548] In some embodiments, the bacteria are *Veillonella* bacteria. In some embodiments, the *Veillonella* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the *Veillonella* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the *Veillonella* bacteria are *Veillonella* bacteria deposited as ATCC designation number PTA-125691.

[0549] In some embodiments, the bacteria are from *Ruminococcus gnavus* bacteria. In some embodiments, the *Ruminococcus gnavus* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695.

[0550] In some embodiments, the bacteria are *Megasphaera sp.* bacteria. In some embodiments, the *Megasphaera sp.* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some embodiments, the *Megasphaera sp.* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some embodiments, the *Megasphaera sp.* bacteria are *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770.

[0551] In some embodiments, the bacteria are *Fournierella massiliensis* bacteria. In some embodiments, the *Fournierella massiliensis* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide

sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696.

[0552] In some embodiments, the bacteria are *Harryflintia acetispora* bacteria. In some embodiments, the *Harryflintia acetispora* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694.

[0553] In some embodiments, the bacteria are of the family *Acidaminococcaceae*, *Alcaligenaceae*, *Akkermansiaceae*, *Bacteriodaceae*, *Bifidobacteriaceae*, *Burkholderiaceae*, *Catabacteriaceae*, *Clostridiaceae*, *Coriobacteriaceae*, *Enterobacteriaceae*, *Enterococcaceae*, *Fusobacteriaceae*, *Lachnospiraceae*, *Listeraceae*, *Mycobacteriaceae*, *Neisseriaceae*, *Odoribacteraceae*, *Oscillospiraceae*, *Peptococcaceae*, *Peptostreptococcaceae*, *Porphyromonadaceae*, *Prevotellaceae*, *Propionibacteraceae*, *Rikenellaceae*, *Ruminococcaceae*, *Selenomonadaceae*, *Sporomusaceae*, *Streptococcaceae*, *Streptomycetaceae*, *Sutterellaceae*, *Synergistaceae*, or *Veillonellaceae*.

[0554] In some embodiments, the bacteria are of the genus *Akkermansia*, *Christensenella*, *Blautia*, *Enterococcus*, *Eubacterium*, *Roseburia*, *Bacteroides*, *Parabacteroides*, or *Erysipelatoclostridium*.

[0555] In some embodiments, the bacteria are *Blautia hydrogenotrophica*, *Blautia stercoris*, *Blautia wexlerae*, *Eubacterium faecium*, *Eubacterium contortum*, *Eubacterium rectale*, *Enterococcus faecalis*, *Enterococcus durans*, *Enterococcus villorum*, *Enterococcus gallinarum*; *Bifidobacterium lactis*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, *Bifidobacterium animalis*, or *Bifidobacterium breve* bacteria.

[0556] In some embodiments, the bacteria are *BCG (bacillus Calmette-Guerin)*, *Parabacteroides*, *Blautia*, *Veillonella*, *Lactobacillus salivarius*, *Agathobaculum*,

Ruminococcus gnavus, *Paraclostridium benzoelyticum*, *Turicibacter sanguinus*, *Burkholderia*, *Klebsiella quasipneumoniae* ssp *similpneumoniae*, *Klebsiella oxytoca*, *Tyzzerelex nexilis*, or *Neisseria* bacteria.

- [0557] In some embodiments, the bacteria are *Blautia hydrogenotrophica* bacteria.
- [0558] In some embodiments, the bacteria are *Blautia stercoris* bacteria.
- [0559] In some embodiments, the bacteria are *Blautia wexlerae* bacteria.
- [0560] In some embodiments, the bacteria are *Enterococcus gallinarum* bacteria.
- [0561] In some embodiments, the bacteria are *Enterococcus faecium* bacteria.
- [0562] In some embodiments, the bacteria are *Bifidobacterium bifidum* bacteria.
- [0563] In some embodiments, the bacteria are *Bifidobacterium breve* bacteria.
- [0564] In some embodiments, the bacteria are *Bifidobacterium longum* bacteria.
- [0565] In some embodiments, the bacteria are *Roseburia hominis* bacteria.
- [0566] In some embodiments, the bacteria are *Bacteroides thetaiotaomicron* bacteria.
- [0567] In some embodiments, the bacteria are *Bacteroides coprocola* bacteria.
- [0568] In some embodiments, the bacteria are *Erysipelatoclostridium ramosum* bacteria.
- [0569] In some embodiments, the bacteria are *Megasphaera massiliensis* bacteria.
- [0570] In some embodiments, the bacteria are *Eubacterium* bacteria.
- [0571] In some embodiments, the bacteria are *Parabacteroides distasonis* bacteria.
- [0572] In some embodiments, the bacteria are *Lactobacillus plantarum* bacteria.
- [0573] In some embodiments, the bacteria are bacteria of the *Negativicutes* class.
- [0574] In some embodiments, the bacteria are of the *Veillonellaceae* family.
- [0575] In some embodiments, the bacteria are of the *Selenomonadaceae* family.
- [0576] In some embodiments, the bacteria are of the *Acidaminococcaceae* family.
- [0577] In some embodiments, the bacteria are of the *Sporomusaceae* family.
- [0578] In some embodiments, the bacteria are of the *Megasphaera* genus.
- [0579] In some embodiments, the bacteria are of the *Selenomonas* genus.
- [0580] In some embodiments, the bacteria are of the *Propionospora* genus.
- [0581] In some embodiments, the bacteria are of the *Acidaminococcus* genus.
- [0582] In some embodiments, the bacteria are *Megasphaera* sp. bacteria.
- [0583] In some embodiments, the bacteria are *Selenomonas felix* bacteria.
- [0584] In some embodiments, the bacteria are *Acidaminococcus intestini* bacteria.

- [0585] In some embodiments, the bacteria are *Propionospora sp.* bacteria.
- [0586] In some embodiments, the bacteria are bacteria of the *Clostridia* class.
- [0587] In some embodiments, the bacteria are of the *Oscillospiraceae* family.
- [0588] In some embodiments, the bacteria are of the *Faecalibacterium* genus.
- [0589] In some embodiments, the bacteria are of the *Fournierella* genus.
- [0590] In some embodiments, the bacteria are of the *Harryflintia* genus.
- [0591] In some embodiments, the bacteria are of the *Agathobaculum* genus.
- [0592] In some embodiments, the bacteria are *Faecalibacterium prausnitzii* (e.g., *Faecalibacterium prausnitzii* Strain A) bacteria.
- [0593] In some embodiments, the bacteria are *Fournierella massiliensis* (e.g., *Fournierella massiliensis* Strain A) bacteria.
- [0594] In some embodiments, the bacteria are *Harryflintia acetispora* (e.g., *Harryflintia acetispora* Strain A) bacteria.
- [0595] In some embodiments, the bacteria are *Agathobaculum sp.* (e.g., *Agathobaculum sp.* Strain A) bacteria.
- [0596] In some embodiments, the bacteria are a strain of *Agathobaculum sp.* In some embodiments, the *Agathobaculum sp.* strain is a strain comprising at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity (e.g., at least 99.5% sequence identity, at least 99.6% sequence identity, at least 99.7% sequence identity, at least 99.8% sequence identity, at least 99.9% sequence identity) to the nucleotide sequence (e.g., genomic sequence, 16S sequence, CRISPR sequence) of the *Agathobaculum sp.* Strain A (ATCC Deposit Number PTA-125892). In some embodiments, the *Agathobaculum sp.* strain is the *Agathobaculum sp.* Strain A (ATCC Deposit Number PTA-125892).
- [0597] In some embodiments, the bacteria are of the class *Bacteroidia* [phylum *Bacteroidota*]. In some embodiments, the bacteria are of order *Bacteroidales*. In some embodiments, the bacteria are of the family *Porphyromonadaceae*. In some embodiments, the bacteria are of the family *Prevotellaceae*. In some embodiments, the bacteria are of the class *Bacteroidia* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the bacteria are of the class *Bacteroidia* that stain Gram negative. In some embodiments, the bacteria are of the class *Bacteroidia* wherein the bacteria is diderm and the bacteria stain Gram negative.

[0598] In some embodiments, the bacteria are of the class *Clostridia* [phylum *Firmicutes*]. In some embodiments, the bacteria are of the order *Eubacteriales*. In some embodiments, the bacteria are of the family *Oscillispiraceae*. In some embodiments, the bacteria are of the family *Lachnospiraceae*. In some embodiments, the bacteria are of the family *Peptostreptococcaceae*. In some embodiments, the bacteria are of the family *Clostridiales* family XIII/ *Incertae sedis* 41. In some embodiments, the bacteria are of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm. In some embodiments, the bacteria are of the class *Clostridia* that stain Gram negative. In some embodiments, the bacteria are of the class *Clostridia* that stain Gram positive. In some embodiments, the bacteria are of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram negative. In some embodiments, the bacteria are of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram positive.

[0599] In some embodiments, the bacteria are of the class *Negativicutes* [phylum *Firmicutes*]. In some embodiments, the bacteria are of the order *Veillonellales*. In some embodiments, the bacteria are of the family *Veillonelloceae*. In some embodiments, the bacteria are of the order *Selenomonadales*. In some embodiments, the bacteria are of the family *Selenomonadaceae*. In some embodiments, the bacteria are of the family *Sporomusaceae*. In some embodiments, the bacteria are of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the bacteria are of the class *Negativicutes* that stain Gram negative. In some embodiments, the bacteria are of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[0600] In some embodiments, the bacteria are of the class *Synergistia* [phylum *Synergistota*]. In some embodiments, the bacteria are of the order *Synergistales*. In some embodiments, the bacteria are of the family *Synergistaceae*. In some embodiments, the bacteria are of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the bacteria are of the class *Synergistia* that stain Gram negative. In some embodiments, the bacteria are of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[0601] In some embodiments, the bacteria are bacteria that produce metabolites, e.g., the bacteria produce butyrate, iosine, propionate, or tryptophan metabolites.

[0602] In some embodiments, the bacteria produce butyrate. In some embodiments, the bacteria are from the genus *Blautia*; *Christensenella*; *Copracoccus*; *Eubacterium*; *Lachnospiraceae*; *Megasphaera*; or *Roseburia*.

[0603] In some embodiments, the bacteria produce isosine. In some embodiments, the bacteria are from the genus *Bifidobacterium*; *Lactobacillus*; or *Olsenella*.

[0604] In some embodiments, the bacteria produce propionate. In some embodiments, the bacteria are from the genus *Akkermansia*; *Bacteriodes*; *Dialister*; *Eubacterium*; *Megasphaera*; *Parabacteriodes*; *Prevotella*; *Ruminococcus*; or *Veillonella*.

[0605] In some embodiments, the bacteria produce tryptophan metabolites. In some embodiments, the bacteria are from the genus *Lactobacillus* or *Peptostreptococcus*.

[0606] In some embodiments, the bacteria are bacteria that produce inhibitors of histone deacetylase 3 (HDAC3). In some embodiments, the bacteria are from the species *Bariatricus massiliensis*, *Faecalibacterium prausnitzii*, *Megasphaera massiliensis* or *Roseburia intestinalis*.

[0607] In some embodiments, the pharmaceutical agent comprises isolated mEVs (e.g., from one or more strains of bacteria (e.g., bacteria of interest)) (e.g., a therapeutically effective amount thereof). E.g., wherein at least 50%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% of the content of the pharmaceutical agent is isolated mEV of bacteria (e.g., bacteria of interest).

[0608] In some embodiments, the pharmaceutical agent comprises mEVs and the mEVs comprise secreted mEVs (smEVs).

[0609] In some embodiments, the pharmaceutical agent comprises mEVs and the mEVs comprise processed mEVs (pmEVs).

[0610] In some embodiments, the pharmaceutical agent comprises pmEVs and the pmEVs are produced from bacteria that have been gamma irradiated, UV irradiated, heat inactivated, acid treated, or oxygen sparged.

[0611] In some embodiments, the pharmaceutical agent comprises pmEVs and the pmEVs are produced from live bacteria.

[0612] In some embodiments, the pharmaceutical agent comprises pmEVs and the pmEVs are produced from dead bacteria.

[0613] In some embodiments, the pharmaceutical agent comprises pmEVs and the pmEVs are produced from non-replicating bacteria.

- [0614] In some embodiments, the pharmaceutical agent comprises mEVs and the mEVs are from one strain of bacteria.
- [0615] In some embodiments, the mEVs are lyophilized (e.g., the lyophilized product further comprises a pharmaceutically acceptable excipient).
- [0616] In some embodiments, the mEVs are gamma irradiated.
- [0617] In some embodiments, the mEVs are UV irradiated.
- [0618] In some embodiments, the mEVs are heat inactivated (e.g., at 50°C for two hours or at 90°C for two hours).
- [0619] In some embodiments, the mEVs are acid treated.
- [0620] In some embodiments, the mEVs are oxygen sparged (e.g., at 0.1 vvm for two hours).
- [0621] In some embodiments, the mEVs are from Gram positive bacteria.
- [0622] In some embodiments, the mEVs are from Gram negative bacteria.
- [0623] In some embodiments, the mEVs are from aerobic bacteria.
- [0624] In some embodiments, the mEVs are from anaerobic bacteria. In some embodiments, the anaerobic bacteria comprise obligate anaerobes. In some embodiments, the anaerobic bacteria comprise facultative anaerobes.
- [0625] In some embodiments, the mEVs are from acidophile bacteria.
- [0626] In some embodiments, the mEVs are from alkaliphile bacteria.
- [0627] In some embodiments, the mEVs are from neutralophile bacteria.
- [0628] In some embodiments, the mEVs are from fastidious bacteria.
- [0629] In some embodiments, the mEVs are from nonfastidious bacteria.
- [0630] In some embodiments, the bacteria are of a taxonomic group (e.g., class, order, family, genus, species or strain) listed in Table 1, Table 2, or Table 3.
- [0631] In some embodiments, the bacteria are a bacterial strain listed in Table 1, Table 2, or Table 3.
- [0632] In some embodiments, the bacteria are of a taxonomic group (e.g., class, order, family, genus, species or strain) listed in Table J.
- [0633] In some embodiments, the bacteria are a bacterial strain listed in Table J.
- [0634] In some embodiments, the Gram negative bacteria belong to class *Negativicutes*.
- [0635] In some embodiments, the Gram negative bacteria belong to family *Veillonellaceae*, *Selenomonadaceae*, *Acidaminococcaceae*, or *Sporomusaceae*.

- [0636] In some embodiments, the mEVs are from bacteria of the genus *Megasphaera*, *Selenomonas*, *Propionospora*, or *Acidaminococcus*.
- [0637] In some embodiments, the mEVs are *Megasphaera sp.*, *Selenomonas felix*, *Acidaminococcus intestine*, or *Propionospora sp.* bacteria.
- [0638] In some embodiments, the mEVs are from bacteria of the genus *Lactococcus*, *Prevotella*, *Bifidobacterium*, or *Veillonella*.
- [0639] In some embodiments, the mEVs are from *Lactococcus lactis cremoris* bacteria.
- [0640] In some embodiments, the mEVs are from *Prevotella histicola* bacteria.
- [0641] In some embodiments, the mEVs are from *Bifidobacterium animalis* bacteria.
- [0642] In some embodiments, the mEVs are from *Veillonella parvula* bacteria.
- [0643] In some embodiments, the mEVs are from *Lactococcus lactis cremoris* bacteria. In some embodiments, the *Lactococcus lactis cremoris* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the *Lactococcus* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the *Lactococcus* bacteria are from *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368).
- [0644] In some embodiments, the mEVs are from *Prevotella* bacteria. In some embodiments, the *Prevotella* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Prevotella* Strain B 50329 (NRRL accession number B 50329). In some embodiments, the *Prevotella* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Prevotella* Strain B 50329 (NRRL accession number B 50329). In some embodiments, the *Prevotella* bacteria are from *Prevotella* Strain B 50329 (NRRL accession number B 50329).
- [0645] In some embodiments, the mEVs are from *Bifidobacterium* bacteria. In some embodiments, the *Bifidobacterium* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097. In some

embodiments, the *Bifidobacterium* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097. In some embodiments, the *Bifidobacterium* bacteria are from *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097.

[0646] In some embodiments, the mEVs are from *Veillonella* bacteria. In some embodiments, the *Veillonella* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the *Veillonella* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the *Veillonella* bacteria are from *Veillonella* bacteria deposited as ATCC designation number PTA-125691.

[0647] In some embodiments, the mEVs are from *Ruminococcus gnavus* bacteria. In some embodiments, the *Ruminococcus gnavus* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are from *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695.

[0648] In some embodiments, the mEVs are from *Megasphaera sp.* bacteria. In some embodiments, the *Megasphaera sp.* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some embodiments, the *Megasphaera sp.* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some embodiments, the *Megasphaera sp.* bacteria are from *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770.

[0649] In some embodiments, the mEVs are from *Fournierella massiliensis* bacteria. In some embodiments, the *Fournierella massiliensis* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are from *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696.

[0650] In some embodiments, the mEVs are from *Harryflintia acetispora* bacteria. In some embodiments, the *Harryflintia acetispora* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are from *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694.

[0651] In some embodiments, the mEVs are from bacteria of the family *Acidaminococcaceae*, *Alcaligenaceae*, *Akkermansiaceae*, *Bacteriodaceae*, *Bifidobacteriaceae*, *Burkholderiaceae*, *Catabacteriaceae*, *Clostridiaceae*, *Coriobacteriaceae*, *Enterobacteriaceae*, *Enterococcaceae*, *Fusobacteriaceae*, *Lachnospiraceae*, *Listeraceae*, *Mycobacteriaceae*, *Neisseriaceae*, *Odoribacteraceae*, *Oscillospiraceae*, *Peptococcaceae*, *Peptostreptococcaceae*, *Porphyromonadaceae*, *Prevotellaceae*, *Propionibacteraceae*, *Rikenellaceae*, *Ruminococcaceae*, *Selenomonadaceae*, *Sporomusaceae*, *Streptococcaceae*, *Streptomycetaceae*, *Sutterellaceae*, *Synergistaceae*, or *Veillonellaceae*.

[0652] In some embodiments, the mEVs are from bacteria of the genus *Akkermansia*, *Christensenella*, *Blautia*, *Enterococcus*, *Eubacterium*, *Roseburia*, *Bacteroides*, *Parabacteroides*, or *Erysipelatoclostridium*.

[0653] In some embodiments, the mEVs are from *Blautia hydrogenotrophica*, *Blautia stercoris*, *Blautia wexlerae*, *Eubacterium faecium*, *Eubacterium contortum*,

Eubacterium rectale, *Enterococcus faecalis*, *Enterococcus durans*, *Enterococcus villorum*, *Enterococcus gallinarum*; *Bifidobacterium lactis*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, *Bifidobacterium animalis*, or *Bifidobacterium breve* bacteria.

[0654] In some embodiments, the mEVs are from *BCG (bacillus Calmette-Guerin)*, *Parabacteroides*, *Blautia*, *Veillonella*, *Lactobacillus salivarius*, *Agathobaculum*, *Ruminococcus gnavus*, *Paraclostridium benzoelyticum*, *Turicibacter sanguinus*, *Burkholderia*, *Klebsiella quasipneumoniae ssp simulpneumoniae*, *Klebsiella oxytoca*, *Tyzzerelex nexilis*, or *Neisseria* bacteria.

[0655] In some embodiments, the mEVs are from *Blautia hydrogenotrophica* bacteria.

[0656] In some embodiments, the mEVs are from *Blautia stercoris* bacteria.

[0657] In some embodiments, the mEVs are from *Blautia wexlerae* bacteria.

[0658] In some embodiments, the mEVs are from *Enterococcus gallinarum* bacteria.

[0659] In some embodiments, the mEVs are from *Enterococcus faecium* bacteria.

[0660] In some embodiments, the mEVs are from *Bifidobacterium bifidum* bacteria.

[0661] In some embodiments, the mEVs are from *Bifidobacterium breve* bacteria.

[0662] In some embodiments, the mEVs are from *Bifidobacterium longum* bacteria.

[0663] In some embodiments, the mEVs are from *Roseburia hominis* bacteria.

[0664] In some embodiments, the mEVs are from *Bacteroides thetaiotaomicron* bacteria.

[0665] In some embodiments, the mEVs are from *Bacteroides coprocola* bacteria.

[0666] In some embodiments, the mEVs are from *Erysipelatoclostridium ramosum* bacteria.

[0667] In some embodiments, the mEVs are from *Megasphaera massiliensis* bacteria.

[0668] In some embodiments, the mEVs are from *Eubacterium* bacteria.

[0669] In some embodiments, the mEVs are from *Parabacteroides distasonis* bacteria.

[0670] In some embodiments, the mEVs are from *Lactobacillus plantarum* bacteria.

[0671] In some embodiments, the mEVs are from bacteria of the *Negativicutes* class.

- [0672] In some embodiments, the mEVs are from bacteria of the *Veillonellaceae* family.
- [0673] In some embodiments, the mEVs are from bacteria of the *Selenomonadaceae* family.
- [0674] In some embodiments, the mEVs are from bacteria of the *Acidaminococcaceae* family.
- [0675] In some embodiments, the mEVs are from bacteria of the *Sporomusaceae* family.
- [0676] In some embodiments, the mEVs are from bacteria of the *Megasphaera* genus.
- [0677] In some embodiments, the mEVs are from bacteria of the *Selenomonas* genus.
- [0678] In some embodiments, the mEVs are from bacteria of the *Propionospora* genus.
- [0679] In some embodiments, the mEVs are from bacteria of the *Acidaminococcus* genus.
- [0680] In some embodiments, the mEVs are from *Megasphaera sp.* bacteria.
- [0681] In some embodiments, the mEVs are from *Selenomonas felix* bacteria.
- [0682] In some embodiments, the mEVs are from *Acidaminococcus intestini* bacteria.
- [0683] In some embodiments, the mEVs are from *Propionospora sp.* bacteria.
- [0684] In some embodiments, the mEVs are from bacteria of the *Clostridia* class.
- [0685] In some embodiments, the mEVs are from bacteria of the *Oscillospiraceae* family.
- [0686] In some embodiments, the mEVs are from bacteria of the *Faecalibacterium* genus.
- [0687] In some embodiments, the mEVs are from bacteria of the *Fournierella* genus.
- [0688] In some embodiments, the mEVs are from bacteria of the *Harryflintia* genus.
- [0689] In some embodiments, the mEVs are from bacteria of the *Agathobaculum* genus.
- [0690] In some embodiments, the mEVs are from *Faecalibacterium prausnitzii* (e.g., *Faecalibacterium prausnitzii* Strain A) bacteria.

[0691] In some embodiments, the mEVs are from *Fournierella massiliensis* (e.g., *Fournierella massiliensis* Strain A) bacteria.

[0692] In some embodiments, the mEVs are from *Harryflintia acetispora* (e.g., *Harryflintia acetispora* Strain A) bacteria.

[0693] In some embodiments, the mEVs are from *Agathobaculum sp.* (e.g., *Agathobaculum sp.* Strain A) bacteria.

[0694] In some embodiments, the mEVs are from a strain of *Agathobaculum sp.* In some embodiments, the *Agathobaculum sp.* strain is a strain comprising at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity (e.g., at least 99.5% sequence identity, at least 99.6% sequence identity, at least 99.7% sequence identity, at least 99.8% sequence identity, at least 99.9% sequence identity) to the nucleotide sequence (e.g., genomic sequence, 16S sequence, CRISPR sequence) of the *Agathobaculum sp.* Strain A (ATCC Deposit Number PTA-125892). In some embodiments, the *Agathobaculum sp.* strain is the *Agathobaculum sp.* Strain A (ATCC Deposit Number PTA-125892).

[0695] In some embodiments, the mEVs are from bacteria of the class *Bacteroidia* [phylum *Bacteroidota*]. In some embodiments, the mEVs are from bacteria of order *Bacteroidales*. In some embodiments, the mEVs are from bacteria of the family *Porphyromonadaceae*. In some embodiments, the mEVs are from bacteria of the family *Prevotellaceae*. In some embodiments, the mEVs are from bacteria of the class *Bacteroidia* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the mEVs are from bacteria of the class *Bacteroidia* that stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Bacteroidia* wherein the bacteria is diderm and the bacteria stain Gram negative.

[0696] In some embodiments, the mEVs are from bacteria of the class *Clostridia* [phylum *Firmicutes*]. In some embodiments, the mEVs are from bacteria of the order *Eubacteriales*. In some embodiments, the mEVs are from bacteria of the family *Oscillispiraceae*. In some embodiments, the mEVs are from bacteria of the family *Lachnospiraceae*. In some embodiments, the mEVs are from bacteria of the family *Peptostreptococcaceae*. In some embodiments, the mEVs are from bacteria of the family *Clostridiales* family XIII/*Incertae sedis* 41. In some embodiments, the mEVs are from bacteria of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm. In some embodiments, the mEVs are from bacteria of the class *Clostridia* that

stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Clostridia* that stain Gram positive. In some embodiments, the mEVs are from bacteria of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram positive.

[0697] In some embodiments, the mEVs are from bacteria of the class *Negativicutes* [phylum *Firmicutes*]. In some embodiments, the mEVs are from bacteria of the order *Veillonellales*. In some embodiments, the mEVs are from bacteria of the family *Veillonelloceae*. In some embodiments, the mEVs are from bacteria of the order *Selenomonadales*. In some embodiments, the mEVs are from bacteria of the family *Selenomonadaceae*. In some embodiments, the mEVs are from bacteria of the family *Sporomusaceae*. In some embodiments, the mEVs are from bacteria of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the mEVs are from bacteria of the class *Negativicutes* that stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[0698] In some embodiments, the mEVs are from bacteria of the class *Synergistia* [phylum *Synergistota*]. In some embodiments, the mEVs are from bacteria of the order *Synergistales*. In some embodiments, the mEVs are from bacteria of the family *Synergistaceae*. In some embodiments, the mEVs are from bacteria of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the mEVs are from bacteria of the class *Synergistia* that stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[0699] In some embodiments, the mEVs are from bacteria that produce metabolites, e.g., the bacteria produce butyrate, iosine, proprionate, or tryptophan metabolites.

[0700] In some embodiments, the bacteria produce butyrate. In some embodiments, the bacteria are from the genus *Blautia*; *Christensella*; *Copracoccus*; *Eubacterium*; *Lachnosperacea*; *Megasphaera*; or *Roseburia*.

[0701] In some embodiments, the bacteria produce iosine. In some embodiments, the bacteria are from the genus *Bifidobacterium*; *Lactobacillus*; or *Olsenella*.

[0702] In some embodiments, the bacteria produce propionate. In some embodiments, the bacteria are from the genus *Akkermansia*; *Bacteriodes*; *Dialister*; *Eubacterium*; *Megasphaera*; *Parabacteriodes*; *Prevotella*; *Ruminococcus*; or *Veillonella*.

[0703] In some embodiments, the bacteria produce tryptophan metabolites. In some embodiments, the bacteria are from the genus *Lactobacillus* or *Peptostreptococcus*.

[0704] In some embodiments, the mEVs are from bacteria that produce inhibitors of histone deacetylase 3 (HDAC3). In some embodiments, the bacteria are from the species *Bariatricus massiliensis*, *Faecalibacterium prausnitzii*, *Megasphaera massiliensis* or *Roseburia intestinalis*.

[0705] In some embodiments, the pharmaceutical agent comprises bacteria and the dose of bacteria is about 1×10^7 to about 2×10^{12} (e.g., about 3×10^{10} or about 1.5×10^{11} or about 1.5×10^{12}) cells (e.g., wherein cell number is determined by total cell count, which is determined by Coulter counter), wherein the dose is per capsule. In some embodiments, the pharmaceutical agent comprises bacteria and the dose of bacteria is about 1×10^{10} to about 2×10^{12} (e.g., about 1.6×10^{11} or about 8×10^{11} or about 9.6×10^{11} or about 12.8×10^{11} or about 1.6×10^{12}) cells (e.g., wherein cell number is determined by total cell count, which is determined by Coulter counter), wherein the dose is per capsule.

[0706] In some embodiments, the pharmaceutical agent comprises bacteria and the dose of bacteria is about 1×10^9 , about 3×10^9 , about 5×10^9 , about 1.5×10^{10} , about 3×10^{10} , about 5×10^{10} , about 1.5×10^{11} , about 1.5×10^{12} , or about 2×10^{12} cells, wherein the dose is per capsule.

[0707] In some embodiments, the pharmaceutical agent comprises mEVs and the dose of mEVs is about 1×10^5 to about 7×10^{13} particles (e.g., wherein particle count is determined by NTA (nanoparticle tracking analysis)), wherein the dose is per capsule or tablet or per total number of minitabets in a capsule. In some embodiments, the pharmaceutical agent comprises mEVs and the dose of mEVs is about 1×10^{10} to about 7×10^{13} particles (e.g., wherein particle count is determined by NTA (nanoparticle tracking analysis)), wherein the dose is per capsule.

[0708] In some embodiments, the pharmaceutical agent comprises bacteria and/or mEVs and the dose of pharmaceutical agent (e.g., bacteria and/or mEVs) is about 10 mg to about 3500 mg, wherein the dose is per tablet.

[0709] In some embodiments, the pharmaceutical agent comprises bacteria and/or mEVs and the dose of drug substance that contains the pharmaceutical agent (e.g., bacteria

and/or mEVs) is about 30 mg to about 1300 mg (by weight of bacteria and/or mEVs) (about 25, about 30, about 35, about 50, about 75, about 100, about 120, about 150, about 250, about 300, about 350, about 400, about 500, about 600, about 700, about 750, about 800, about 900, about 1000, about 1100, about 1200, about 1250, about 1300, about 2000, about 2500, about 3000, or about 3500 mg, wherein the dose is per capsule.

[0710] In some embodiments, the pharmaceutical agent comprises bacteria and/or mEVs and the dose of pharmaceutical agent (e.g., bacteria and/or mEVs) is about 2×10^6 to about 2×10^{16} particles (e.g., wherein particle count is determined by NTA (nanoparticle tracking analysis)), wherein the dose is per capsule.

[0711] In some embodiments, the pharmaceutical agent comprises bacteria and/or mEVs and the dose of pharmaceutical agent (e.g., bacteria and/or mEVs) is about 5 mg to about 900 mg total protein (e.g., wherein total protein is determined by Bradford assay or BCA), wherein the dose is per capsule.

[0712] In some embodiments, the can be (or be present in) a medicinal product, medical food, a food product, or a dietary supplement.

[0713] In some embodiments, the solid dosage form further comprises one or more additional pharmaceutical agents.

[0714] In some embodiments, the solid dosage form further comprises an excipient (e.g., an excipient described herein, e.g., a diluent, a binder and/or an adhesive, a disintegrant, a lubricant and/or a glidant, a coloring agent, a flavoring agent, and/or a sweetening agent).

[0715] In some aspects, the disclosure provides a method for preparing an enterically coated tablet comprising a pharmaceutical agent (e.g., a therapeutically effective amount thereof), wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), the method comprising:

[0716] a) combining the pharmaceutical agent with a pharmaceutically acceptable excipient;

[0717] b) compressing the pharmaceutical agent and pharmaceutically acceptable excipient, thereby forming a tablet; and

[0718] c) enterically coating the tablet, thereby preparing the enterically coated tablet.

[0719] In some embodiments, the tablet (e.g., enterically coated tablet) is a 5mm, 6mm, 7mm, 8mm, 9mm, 10mm, 11mm, 12mm, 13mm, 14mm, 15mm, 16mm, 17mm, or 18mm tablet.

[0720] In some embodiments, the enteric coating comprises one enteric coating.

[0721] In some embodiments, the enteric coating comprises an inner enteric coating and an outer enteric coating, and wherein the inner and outer enteric coatings are not identical (e.g., the inner and outer enteric coatings do not contain identical components in identical amounts).

[0722] In some embodiments, the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) comprises a polymethacrylate-based copolymer.

[0723] In some embodiments, the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) comprises a methacrylic acid ethyl acrylate (MAE) copolymer (1:1).

[0724] In some embodiments, the one enteric coating comprises a methacrylic acid ethyl acrylate (MAE) copolymer (1:1) (such as Kollicoat MAE 100P).

[0725] In some embodiments, the one enteric coating comprises a Eudragit copolymer, e.g., a Eudragit L (e.g., Eudragit L 100-55; Eudragit L 30 D-55), a Eudragit S, a Eudragit RL, a Eudragit RS, a Eudragit E, or a Eudragit FS (e.g., Eudragit FS 30 D).

[0726] In some embodiments, the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) comprises cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), poly(vinyl acetate phthalate) (PVAP), hydroxypropyl methylcellulose phthalate (HPMCP), a fatty acid, a wax, shellac (esters of aleuritic acid), a plastic, a plant fiber, zein, Aqua-Zein (an aqueous zein formulation containing no alcohol), amylose starch, a starch derivative, a dextrin, a methyl acrylate-methacrylic acid copolymer, cellulose acetate succinate, hydroxypropyl methyl cellulose acetate succinate (hypromellose acetate succinate), a methyl methacrylate-methacrylic acid copolymer, or sodium alginate.

[0727] In some embodiments, the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) comprises an anionic polymeric material.

[0728] In some embodiments, the pharmaceutical agent comprises bacteria.

[0729] In some embodiments, the pharmaceutical agent comprises microbial extracellular vesicles (mEV).

[0730] In some embodiments, the pharmaceutical agent comprises bacteria and microbial extracellular vesicles (mEV).

[0731] In some embodiments, the pharmaceutical agent has one or more beneficial immune effects outside the gastrointestinal tract, e.g., when the solid dosage form is orally administered.

[0732] In some embodiments, the pharmaceutical agent modulates immune effects outside the gastrointestinal tract (e.g., outside of the small intestine) in the subject, e.g., when the solid dosage form is orally administered.

[0733] In some embodiments, the pharmaceutical agent causes a systemic effect (e.g., an effect outside of the gastrointestinal tract), e.g., when the solid dosage form is orally administered.

[0734] In some embodiments, the pharmaceutical agent acts on immune cells and/or epithelial cells in the small intestine (e.g., causing a systemic effect (e.g., an effect outside of the gastrointestinal tract), e.g., when the solid dosage form is orally administered.

[0735] In some embodiments, the pharmaceutical agent comprises isolated bacteria (e.g., from one or more strains of bacteria (e.g., bacteria of interest) (e.g., a therapeutically effective amount thereof)). E.g., wherein at least 50%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% of the content of the pharmaceutical agent is the isolated bacteria (e.g., bacteria of interest).

[0736] In some embodiments, the pharmaceutical agent comprises bacteria that have been gamma irradiated, UV irradiated, heat inactivated, acid treated, or oxygen sparged.

[0737] In some embodiments, the pharmaceutical agent comprises live bacteria.

[0738] In some embodiments, the pharmaceutical agent comprises dead bacteria.

[0739] In some embodiments, the pharmaceutical agent comprises non-replicating bacteria.

[0740] In some embodiments, the pharmaceutical agent comprises bacteria from one strain of microbe (e.g., bacteria).

[0741] In some embodiments, the bacteria are lyophilized (e.g., the lyophilized product further comprises a pharmaceutically acceptable excipient) (e.g., a powder form).

[0742] In some embodiments, the bacteria are gamma irradiated.

- [0743] In some embodiments, the bacteria are UV irradiated.
- [0744] In some embodiments, the bacteria are heat inactivated (e.g., at 50°C for two hours or at 90°C for two hours).
- [0745] In some embodiments, the bacteria are acid treated.
- [0746] In some embodiments, the bacteria are oxygen sparged (e.g., at 0.1 vvm for two hours).
- [0747] In some embodiments, the bacteria are Gram positive bacteria.
- [0748] In some embodiments, the bacteria are Gram negative bacteria.
- [0749] In some embodiments, the bacteria are aerobic bacteria.
- [0750] In some embodiments, the bacteria are anaerobic bacteria. In some embodiments, the anaerobic bacteria comprise obligate anaerobes. In some embodiments, the anaerobic bacteria comprise facultative anaerobes.
- [0751] In some embodiments, the bacteria are acidophile bacteria.
- [0752] In some embodiments, the bacteria are alkaliphile bacteria.
- [0753] In some embodiments, the bacteria are neutralophile bacteria.
- [0754] In some embodiments, the bacteria are fastidious bacteria.
- [0755] In some embodiments, the bacteria are nonfastidious bacteria.
- [0756] In some embodiments, the bacteria are of a taxonomic group (e.g., class, order, family, genus, species or strain) listed in Table 1, Table 2, or Table 3.
- [0757] In some embodiments, the bacteria are a bacterial strain listed in Table 1, Table 2, or Table 3.
- [0758] In some embodiments, the bacteria are of a taxonomic group (e.g., class, order, family, genus, species or strain) listed in Table J.
- [0759] In some embodiments, the bacteria are a bacterial strain listed in Table J.
- [0760] In some embodiments, the Gram negative bacteria belong to class *Negativicutes*.
- [0761] In some embodiments, the Gram negative bacteria belong to family *Veillonellaceae*, *Selenomonadaceae*, *Acidaminococcaceae*, or *Sporomusaceae*.
- [0762] In some embodiments, the bacteria of the genus *Megasphaera*, *Selenomonas*, *Propionospora*, or *Acidaminococcus*.
- [0763] In some embodiments, the bacteria are *Megasphaera sp.*, *Selenomonas felix*, *Acidaminococcus intestine*, or *Propionospora sp.* bacteria.

[0764] In some embodiments, the bacteria are of the genus *Lactococcus*, *Prevotella*, *Bifidobacterium*, or *Veillonella*.

[0765] In some embodiments, the bacteria are *Lactococcus lactis cremoris* bacteria.

[0766] In some embodiments, the bacteria are *Prevotella histicola* bacteria.

[0767] In some embodiments, the bacteria are *Bifidobacterium animalis* bacteria.

[0768] In some embodiments, the bacteria are *Veillonella parvula* bacteria.

[0769] In some embodiments, the bacteria are *Lactococcus lactis cremoris* bacteria.

In some embodiments, the *Lactococcus lactis cremoris* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the *Lactococcus* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the *Lactococcus* bacteria are *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368).

[0770] In some embodiments, the bacteria are *Prevotella* bacteria. In some embodiments, the *Prevotella* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Prevotella* Strain B 50329 (NRRL accession number B 50329). In some embodiments, the *Prevotella* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Prevotella* Strain B 50329 (NRRL accession number B 50329). In some embodiments, the *Prevotella* bacteria are *Prevotella* Strain B 50329 (NRRL accession number B 50329).

[0771] In some embodiments, the bacteria are *Bifidobacterium* bacteria. In some embodiments, the *Bifidobacterium* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097. In some embodiments, the *Bifidobacterium* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097. In some embodiments, the *Bifidobacterium* bacteria are *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097.

[0772] In some embodiments, the bacteria are *Veillonella* bacteria. In some embodiments, the *Veillonella* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the *Veillonella* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the *Veillonella* bacteria are *Veillonella* bacteria deposited as ATCC designation number PTA-125691.

[0773] In some embodiments, the bacteria are from *Ruminococcus gnavus* bacteria. In some embodiments, the *Ruminococcus gnavus* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695.

[0774] In some embodiments, the bacteria are *Megasphaera sp.* bacteria. In some embodiments, the *Megasphaera sp.* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some embodiments, the *Megasphaera sp.* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some embodiments, the *Megasphaera sp.* bacteria are *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770.

[0775] In some embodiments, the bacteria are *Fournierella massiliensis* bacteria. In some embodiments, the *Fournierella massiliensis* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide

sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696.

[0776] In some embodiments, the bacteria are *Harryflintia acetispora* bacteria. In some embodiments, the *Harryflintia acetispora* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694.

[0777] In some embodiments, the bacteria are of the family *Acidaminococcaceae*, *Alcaligenaceae*, *Akkermansiaceae*, *Bacteriodaceae*, *Bifidobacteriaceae*, *Burkholderiaceae*, *Catabacteriaceae*, *Clostridiaceae*, *Coriobacteriaceae*, *Enterobacteriaceae*, *Enterococcaceae*, *Fusobacteriaceae*, *Lachnospiraceae*, *Listeraceae*, *Mycobacteriaceae*, *Neisseriaceae*, *Odoribacteraceae*, *Oscillospiraceae*, *Peptococcaceae*, *Peptostreptococcaceae*, *Porphyromonadaceae*, *Prevotellaceae*, *Propionibacteraceae*, *Rikenellaceae*, *Ruminococcaceae*, *Selenomonadaceae*, *Sporomusaceae*, *Streptococcaceae*, *Streptomycetaceae*, *Sutterellaceae*, *Synergistaceae*, or *Veillonellaceae*.

[0778] In some embodiments, the bacteria are of the genus *Akkermansia*, *Christensenella*, *Blautia*, *Enterococcus*, *Eubacterium*, *Roseburia*, *Bacteroides*, *Parabacteroides*, or *Erysipelatoclostridium*.

[0779] In some embodiments, the bacteria are *Blautia hydrogenotrophica*, *Blautia stercoris*, *Blautia wexlerae*, *Eubacterium faecium*, *Eubacterium contortum*, *Eubacterium rectale*, *Enterococcus faecalis*, *Enterococcus durans*, *Enterococcus villorum*, *Enterococcus gallinarum*; *Bifidobacterium lactis*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, *Bifidobacterium animalis*, or *Bifidobacterium breve* bacteria.

[0780] In some embodiments, the bacteria are *BCG (bacillus Calmette-Guerin)*, *Parabacteroides*, *Blautia*, *Veillonella*, *Lactobacillus salivarius*, *Agathobaculum*, *Ruminococcus gnavus*, *Paraclostridium benzoelyticum*, *Turicibacter sanguinus*, *Burkholderia*, *Klebsiella quasipneumoniae ssp simulpneumoniae*, *Klebsiella oxytoca*, *Tyzzera nexilis*, or *Neisseria* bacteria.

- [0781] In some embodiments, the bacteria are *Blautia hydrogenotrophica* bacteria.
- [0782] In some embodiments, the bacteria are *Blautia stercoris* bacteria.
- [0783] In some embodiments, the bacteria are *Blautia wexlerae* bacteria.
- [0784] In some embodiments, the bacteria are *Enterococcus gallinarum* bacteria.
- [0785] In some embodiments, the bacteria are *Enterococcus faecium* bacteria.
- [0786] In some embodiments, the bacteria are *Bifidobacterium bifidum* bacteria.
- [0787] In some embodiments, the bacteria are *Bifidobacterium breve* bacteria.
- [0788] In some embodiments, the bacteria are *Bifidobacterium longum* bacteria.
- [0789] In some embodiments, the bacteria are *Roseburia hominis* bacteria.
- [0790] In some embodiments, the bacteria are *Bacteroides thetaiotaomicron* bacteria.
- [0791] In some embodiments, the bacteria are *Bacteroides coprocola* bacteria.
- [0792] In some embodiments, the bacteria are *Erysipelatoclostridium ramosum* bacteria.
- [0793] In some embodiments, the bacteria are *Megasphaera massiliensis* bacteria.
- [0794] In some embodiments, the bacteria are *Eubacterium* bacteria.
- [0795] In some embodiments, the bacteria are *Parabacteroides distasonis* bacteria.
- [0796] In some embodiments, the bacteria are *Lactobacillus plantarum* bacteria.
- [0797] In some embodiments, the bacteria are bacteria of the *Negativicutes* class.
- [0798] In some embodiments, the bacteria are of the *Veillonellaceae* family.
- [0799] In some embodiments, the bacteria are of the *Selenomonadaceae* family.
- [0800] In some embodiments, the bacteria are of the *Acidaminococcaceae* family.
- [0801] In some embodiments, the bacteria are of the *Sporomusaceae* family.
- [0802] In some embodiments, the bacteria are of the *Megasphaera* genus.
- [0803] In some embodiments, the bacteria are of the *Selenomonas* genus.
- [0804] In some embodiments, the bacteria are of the *Propionospora* genus.
- [0805] In some embodiments, the bacteria are of the *Acidaminococcus* genus.
- [0806] In some embodiments, the bacteria are *Megasphaera sp.* bacteria.
- [0807] In some embodiments, the bacteria are *Selenomonas felix* bacteria.
- [0808] In some embodiments, the bacteria are *Acidaminococcus intestini* bacteria.
- [0809] In some embodiments, the bacteria are *Propionospora sp.* bacteria.
- [0810] In some embodiments, the bacteria are bacteria of the *Clostridia* class.
- [0811] In some embodiments, the bacteria are of the *Oscillospiraceae* family.

- [0812] In some embodiments, the bacteria are of the *Faecalibacterium* genus.
- [0813] In some embodiments, the bacteria are of the *Fournierella* genus.
- [0814] In some embodiments, the bacteria are of the *Harryflintia* genus.
- [0815] In some embodiments, the bacteria are of the *Agathobaculum* genus.
- [0816] In some embodiments, the bacteria are *Faecalibacterium prausnitzii* (e.g., *Faecalibacterium prausnitzii* Strain A) bacteria.
- [0817] In some embodiments, the bacteria are *Fournierella massiliensis* (e.g., *Fournierella massiliensis* Strain A) bacteria.
- [0818] In some embodiments, the bacteria are *Harryflintia acetispora* (e.g., *Harryflintia acetispora* Strain A) bacteria.
- [0819] In some embodiments, the bacteria are *Agathobaculum sp.* (e.g., *Agathobaculum sp.* Strain A) bacteria.
- [0820] In some embodiments, the bacteria are a strain of *Agathobaculum sp.* In some embodiments, the *Agathobaculum sp.* strain is a strain comprising at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity (e.g., at least 99.5% sequence identity, at least 99.6% sequence identity, at least 99.7% sequence identity, at least 99.8% sequence identity, at least 99.9% sequence identity) to the nucleotide sequence (e.g., genomic sequence, 16S sequence, CRISPR sequence) of the *Agathobaculum sp.* Strain A (ATCC Deposit Number PTA-125892). In some embodiments, the *Agathobaculum sp.* strain is the *Agathobaculum sp.* Strain A (ATCC Deposit Number PTA-125892).
- [0821] In some embodiments, the bacteria are of the class *Bacteroidia* [phylum *Bacteroidota*]. In some embodiments, the bacteria are of order *Bacteroidales*. In some embodiments, the bacteria are of the family *Porphyromonadaceae*. In some embodiments, the bacteria are of the family *Prevotellaceae*. In some embodiments, the bacteria are of the class *Bacteroidia* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the bacteria are of the class *Bacteroidia* that stain Gram negative. In some embodiments, the bacteria are of the class *Bacteroidia* wherein the bacteria is diderm and the bacteria stain Gram negative.
- [0822] In some embodiments, the bacteria are of the class *Clostridia* [phylum *Firmicutes*]. In some embodiments, the bacteria are of the order *Eubacteriales*. In some embodiments, the bacteria are of the family *Oscillispiraceae*. In some embodiments, the bacteria are of the family *Lachnospiraceae*. In some embodiments, the bacteria are of the

family *Peptostreptococcaceae*. In some embodiments, the bacteria are of the family *Clostridiales* family XIII/*Incertae sedis* 41. In some embodiments, the bacteria are of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm. In some embodiments, the bacteria are of the class *Clostridia* that stain Gram negative. In some embodiments, the bacteria are of the class *Clostridia* that stain Gram positive. In some embodiments, the bacteria are of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram negative. In some embodiments, the bacteria are of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram positive.

[0823] In some embodiments, the bacteria are of the class *Negativicutes* [phylum *Firmicutes*]. In some embodiments, the bacteria are of the order *Veillonellales*. In some embodiments, the bacteria are of the family *Veillonelloceae*. In some embodiments, the bacteria are of the order *Selenomonadales*. In some embodiments, the bacteria are of the family *Selenomonadaceae*. In some embodiments, the bacteria are of the family *Sporomusaceae*. In some embodiments, the bacteria are of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the bacteria are of the class *Negativicutes* that stain Gram negative. In some embodiments, the bacteria are of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[0824] In some embodiments, the bacteria are of the class *Synergistia* [phylum *Synergistota*]. In some embodiments, the bacteria are of the order *Synergistales*. In some embodiments, the bacteria are of the family *Synergistaceae*. In some embodiments, the bacteria are of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the bacteria are of the class *Synergistia* that stain Gram negative. In some embodiments, the bacteria are of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[0825] In some embodiments, the bacteria are bacteria that produce metabolites, e.g., the bacteria produce butyrate, iosine, proprionate, or tryptophan metabolites.

[0826] In some embodiments, the bacteria produce butyrate. In some embodiments, the bacteria are from the genus *Blautia*; *Christensella*; *Copracoccus*; *Eubacterium*; *Lachnosperacea*; *Megasphaera*; or *Roseburia*.

[0827] In some embodiments, the bacteria produce iosine. In some embodiments, the bacteria are from the genus *Bifidobacterium*; *Lactobacillus*; or *Olsenella*.

[0828] In some embodiments, the bacteria produce propionate. In some embodiments, the bacteria are from the genus *Akkermansia*; *Bacteriodes*; *Dialister*; *Eubacterium*; *Megasphaera*; *Parabacteriodes*; *Prevotella*; *Ruminococcus*; or *Veillonella*.

[0829] In some embodiments, the bacteria produce tryptophan metabolites. In some embodiments, the bacteria are from the genus *Lactobacillus* or *Peptostreptococcus*.

[0830] In some embodiments, the bacteria are bacteria that produce inhibitors of histone deacetylase 3 (HDAC3). In some embodiments, the bacteria are from the species *Bariatricus massiliensis*, *Faecalibacterium prausnitzii*, *Megasphaera massiliensis* or *Roseburia intestinalis*.

[0831]

[0832] In some embodiments, the pharmaceutical agent comprises isolated mEVs (e.g., from one or more strains of bacteria (e.g., bacteria of interest)) (e.g., a therapeutically effective amount thereof). E.g., wherein at least 50%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% of the content of the pharmaceutical agent is isolated mEV of bacteria (e.g., bacteria of interest).

[0833] In some embodiments, the pharmaceutical agent comprises mEVs and the mEVs comprise secreted mEVs (smEVs).

[0834] In some embodiments, the pharmaceutical agent comprises mEVs and the mEVs comprise processed mEVs (pmEVs).

[0835] In some embodiments, the pharmaceutical agent comprises pmEVs and the pmEVs are produced from bacteria that have been gamma irradiated, UV irradiated, heat inactivated, acid treated, or oxygen sparged.

[0836] In some embodiments, the pharmaceutical agent comprises pmEVs and the pmEVs are produced from live bacteria.

[0837] In some embodiments, the pharmaceutical agent comprises pmEVs and the pmEVs are produced from dead bacteria.

[0838] In some embodiments, the pharmaceutical agent comprises pmEVs and the pmEVs are produced from non-replicating bacteria.

[0839] In some embodiments, the pharmaceutical agent comprises mEVs and the mEVs are from one strain of bacteria.

[0840] In some embodiments, the mEVs are lyophilized (e.g., the lyophilized product further comprises a pharmaceutically acceptable excipient).

[0841] In some embodiments, the mEVs are gamma irradiated.

- [0842] In some embodiments, the mEVs are UV irradiated.
- [0843] In some embodiments, the mEVs are heat inactivated (e.g., at 50°C for two hours or at 90°C for two hours).
- [0844] In some embodiments, the mEVs are acid treated.
- [0845] In some embodiments, the mEVs are oxygen sparged (e.g., at 0.1 vvm for two hours).
- [0846] In some embodiments, the mEVs are from Gram positive bacteria.
- [0847] In some embodiments, the mEVs are from Gram negative bacteria.
- [0848] In some embodiments, the mEVs are from aerobic bacteria.
- [0849] In some embodiments, the mEVs are from anaerobic bacteria. In some embodiments, the anaerobic bacteria comprise obligate anaerobes. In some embodiments, the anaerobic bacteria comprise facultative anaerobes.
- [0850] In some embodiments, the mEVs are from acidophile bacteria.
- [0851] In some embodiments, the mEVs are from alkaliphile bacteria.
- [0852] In some embodiments, the mEVs are from neutralophile bacteria.
- [0853] In some embodiments, the mEVs are from fastidious bacteria.
- [0854] In some embodiments, the mEVs are from nonfastidious bacteria.
- [0855] In some embodiments, the mEVs are from bacteria of a taxonomic group (e.g., class, order, family, genus, species or strain) listed in Table 1, Table 2, or Table 3.
- [0856] In some embodiments, the mEVs are from a bacterial strain listed in Table 1, Table 2, or Table 3.
- [0857] In some embodiments, the mEVs are from bacteria of a taxonomic group (e.g., class, order, family, genus, species or strain) listed in Table J.
- [0858] In some embodiments, the mEVs are from a bacterial strain listed in Table J.
- [0859] In some embodiments, the Gram negative bacteria belong to class *Negativicutes*.
- [0860] In some embodiments, the Gram negative bacteria belong to family *Veillonellaceae*, *Selenomonadaceae*, *Acidaminococcaceae*, or *Sporomusaceae*.
- [0861] In some embodiments, the mEVs are from bacteria of the genus *Megasphaera*, *Selenomonas*, *Propionospora*, or *Acidaminococcus*.
- [0862] In some embodiments, the mEVs are *Megasphaera sp.*, *Selenomonas felix*, *Acidaminococcus intestine*, or *Propionospora sp.* bacteria.

- [0863] In some embodiments, the mEVs are from bacteria of the genus *Lactococcus*, *Prevotella*, *Bifidobacterium*, or *Veillonella*.
- [0864] In some embodiments, the mEVs are from *Lactococcus lactis cremoris* bacteria.
- [0865] In some embodiments, the mEVs are from *Prevotella histicola* bacteria.
- [0866] In some embodiments, the mEVs are from *Bifidobacterium animalis* bacteria.
- [0867] In some embodiments, the mEVs are from *Veillonella parvula* bacteria.
- [0868] In some embodiments, the mEVs are from *Lactococcus lactis cremoris* bacteria. In some embodiments, the *Lactococcus lactis cremoris* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the *Lactococcus* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the *Lactococcus* bacteria are from *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368).
- [0869] In some embodiments, the mEVs are from *Prevotella* bacteria. In some embodiments, the *Prevotella* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Prevotella* Strain B 50329 (NRRL accession number B 50329). In some embodiments, the *Prevotella* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Prevotella* Strain B 50329 (NRRL accession number B 50329). In some embodiments, the *Prevotella* bacteria are from *Prevotella* Strain B 50329 (NRRL accession number B 50329).
- [0870] In some embodiments, the mEVs are from *Bifidobacterium* bacteria. In some embodiments, the *Bifidobacterium* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097. In some embodiments, the *Bifidobacterium* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097. In some

embodiments, the *Bifidobacterium* bacteria are from *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097.

[0871] In some embodiments, the mEVs are from *Veillonella* bacteria. In some embodiments, the *Veillonella* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the *Veillonella* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the *Veillonella* bacteria are from *Veillonella* bacteria deposited as ATCC designation number PTA-125691.

[0872] In some embodiments, the mEVs are from *Ruminococcus gnavus* bacteria. In some embodiments, the *Ruminococcus gnavus* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are from *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695.

[0873] In some embodiments, the mEVs are from *Megasphaera sp.* bacteria. In some embodiments, the *Megasphaera sp.* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some embodiments, the *Megasphaera sp.* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some embodiments, the *Megasphaera sp.* bacteria are from *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770.

[0874] In some embodiments, the mEVs are from *Fournierella massiliensis* bacteria. In some embodiments, the *Fournierella massiliensis* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Fournierella massiliensis* bacteria deposited as ATCC

designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are from *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696.

[0875] In some embodiments, the mEVs are from *Harryflintia acetispora* bacteria. In some embodiments, the *Harryflintia acetispora* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are from *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694.

[0876] In some embodiments, the mEVs are from bacteria of the family *Acidaminococcaceae*, *Alcaligenaceae*, *Akkermansiaceae*, *Bacteriodaceae*, *Bifidobacteriaceae*, *Burkholderiaceae*, *Catabacteriaceae*, *Clostridiaceae*, *Coriobacteriaceae*, *Enterobacteriaceae*, *Enterococcaceae*, *Fusobacteriaceae*, *Lachnospiraceae*, *Listeraceae*, *Mycobacteriaceae*, *Neisseriaceae*, *Odoribacteraceae*, *Oscillospiraceae*, *Peptococcaceae*, *Peptostreptococcaceae*, *Porphyromonadaceae*, *Prevotellaceae*, *Propionibacteraceae*, *Rikenellaceae*, *Ruminococcaceae*, *Selenomonadaceae*, *Sporomusaceae*, *Streptococcaceae*, *Streptomyetaceae*, *Sutterellaceae*, *Synergistaceae*, or *Veillonellaceae*.

[0877] In some embodiments, the mEVs are from bacteria of the genus *Akkermansia*, *Christensenella*, *Blautia*, *Enterococcus*, *Eubacterium*, *Roseburia*, *Bacteroides*, *Parabacteroides*, or *Erysipelatoclostridium*.

[0878] In some embodiments, the mEVs are from *Blautia hydrogenotrophica*, *Blautia stercoris*, *Blautia wexlerae*, *Eubacterium faecium*, *Eubacterium contortum*, *Eubacterium rectale*, *Enterococcus faecalis*, *Enterococcus durans*, *Enterococcus villorum*, *Enterococcus gallinarum*; *Bifidobacterium lactis*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, *Bifidobacterium animalis*, or *Bifidobacterium breve* bacteria.

- [0879] In some embodiments, the mEVs are from *BCG (bacillus Calmette-Guerin)*, *Parabacteroides*, *Blautia*, *Veillonella*, *Lactobacillus salivarius*, *Agathobaculum*, *Ruminococcus gnavus*, *Paraclostridium benzoelyticum*, *Turicibacter sanguinus*, *Burkholderia*, *Klebsiella quasipneumoniae ssp similpneumoniae*, *Klebsiella oxytoca*, *Tyzzera nexilis*, or *Neisseria* bacteria.
- [0880] In some embodiments, the mEVs are from *Blautia hydrogenotrophica* bacteria.
- [0881] In some embodiments, the mEVs are from *Blautia stercoris* bacteria.
- [0882] In some embodiments, the mEVs are from *Blautia wexlerae* bacteria.
- [0883] In some embodiments, the mEVs are from *Enterococcus gallinarum* bacteria.
- [0884] In some embodiments, the mEVs are from *Enterococcus faecium* bacteria.
- [0885] In some embodiments, the mEVs are from *Bifidobacterium bifidum* bacteria.
- [0886] In some embodiments, the mEVs are from *Bifidobacterium breve* bacteria.
- [0887] In some embodiments, the mEVs are from *Bifidobacterium longum* bacteria.
- [0888] In some embodiments, the mEVs are from *Roseburia hominis* bacteria.
- [0889] In some embodiments, the mEVs are from *Bacteroides thetaiotaomicron* bacteria.
- [0890] In some embodiments, the mEVs are from *Bacteroides coprocola* bacteria.
- [0891] In some embodiments, the mEVs are from *Erysipelatoclostridium ramosum* bacteria.
- [0892] In some embodiments, the mEVs are from *Megasphaera massiliensis* bacteria.
- [0893] In some embodiments, the mEVs are from *Eubacterium* bacteria.
- [0894] In some embodiments, the mEVs are from *Parabacteroides distasonis* bacteria.
- [0895] In some embodiments, the mEVs are from *Lactobacillus plantarum* bacteria.
- [0896] In some embodiments, the mEVs are from bacteria of the *Negativicutes* class.
- [0897] In some embodiments, the mEVs are from bacteria of the *Veillonellaceae* family.

- [0898] In some embodiments, the mEVs are from bacteria of the *Selenomonadaceae* family.
- [0899] In some embodiments, the mEVs are from bacteria of the *Acidaminococcaceae* family.
- [0900] In some embodiments, the mEVs are from bacteria of the *Sporomusaceae* family.
- [0901] In some embodiments, the mEVs are from bacteria of the *Megasphaera* genus.
- [0902] In some embodiments, the mEVs are from bacteria of the *Selenomonas* genus.
- [0903] In some embodiments, the mEVs are from bacteria of the *Propionospora* genus.
- [0904] In some embodiments, the mEVs are from bacteria of the *Acidaminococcus* genus.
- [0905] In some embodiments, the mEVs are from *Megasphaera sp.* bacteria.
- [0906] In some embodiments, the mEVs are from *Selenomonas felix* bacteria.
- [0907] In some embodiments, the mEVs are from *Acidaminococcus intestini* bacteria.
- [0908] In some embodiments, the mEVs are from *Propionospora sp.* bacteria.
- [0909] In some embodiments, the mEVs are from bacteria of the *Clostridia* class.
- [0910] In some embodiments, the mEVs are from bacteria of the *Oscillospiraceae* family.
- [0911] In some embodiments, the mEVs are from bacteria of the *Faecalibacterium* genus.
- [0912] In some embodiments, the mEVs are from bacteria of the *Fournierella* genus.
- [0913] In some embodiments, the mEVs are from bacteria of the *Harryflintia* genus.
- [0914] In some embodiments, the mEVs are from bacteria of the *Agathobaculum* genus.
- [0915] In some embodiments, the mEVs are from *Faecalibacterium prausnitzii* (e.g., *Faecalibacterium prausnitzii* Strain A) bacteria.
- [0916] In some embodiments, the mEVs are from *Fournierella massiliensis* (e.g., *Fournierella massiliensis* Strain A) bacteria.

[0917] In some embodiments, the mEVs are from *Harryflintia acetispora* (e.g., *Harryflintia acetispora* Strain A) bacteria.

[0918] In some embodiments, the mEVs are from *Agathobaculum sp.* (e.g., *Agathobaculum sp.* Strain A) bacteria.

[0919] In some embodiments, the mEVs are from a strain of *Agathobaculum sp.* In some embodiments, the *Agathobaculum sp.* strain is a strain comprising at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity (e.g., at least 99.5% sequence identity, at least 99.6% sequence identity, at least 99.7% sequence identity, at least 99.8% sequence identity, at least 99.9% sequence identity) to the nucleotide sequence (e.g., genomic sequence, 16S sequence, CRISPR sequence) of the *Agathobaculum sp.* Strain A (ATCC Deposit Number PTA-125892). In some embodiments, the *Agathobaculum sp.* strain is the *Agathobaculum sp.* Strain A (ATCC Deposit Number PTA-125892).

[0920] In some embodiments, the mEVs are from bacteria of the class *Bacteroidia* [phylum *Bacteroidota*]. In some embodiments, the mEVs are from bacteria of order *Bacteroidales*. In some embodiments, the mEVs are from bacteria of the family *Porphyromonadaceae*. In some embodiments, the mEVs are from bacteria of the family *Prevotellaceae*. In some embodiments, the mEVs are from bacteria of the class *Bacteroidia* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the mEVs are from bacteria of the class *Bacteroidia* that stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Bacteroidia* wherein the bacteria is diderm and the bacteria stain Gram negative.

[0921] In some embodiments, the mEVs are from bacteria of the class *Clostridia* [phylum *Firmicutes*]. In some embodiments, the mEVs are from bacteria of the order *Eubacteriales*. In some embodiments, the mEVs are from bacteria of the family *Oscillispiraceae*. In some embodiments, the mEVs are from bacteria of the family *Lachnospiraceae*. In some embodiments, the mEVs are from bacteria of the family *Peptostreptococcaceae*. In some embodiments, the mEVs are from bacteria of the family *Clostridiales family XIII/ Incertae sedis 41*. In some embodiments, the mEVs are from bacteria of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm. In some embodiments, the mEVs are from bacteria of the class *Clostridia* that stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Clostridia* that stain Gram positive. In some embodiments, the mEVs are from bacteria of

the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram positive.

[0922] In some embodiments, the mEVs are from bacteria of the class *Negativicutes* [phylum *Firmicutes*]. In some embodiments, the mEVs are from bacteria of the order *Veillonellales*. In some embodiments, the mEVs are from bacteria of the family *Veillonelloceae*. In some embodiments, the mEVs are from bacteria of the order *Selenomonadales*. In some embodiments, the mEVs are from bacteria of the family *Selenomonadaceae*. In some embodiments, the mEVs are from bacteria of the family *Sporomusaceae*. In some embodiments, the mEVs are from bacteria of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the mEVs are from bacteria of the class *Negativicutes* that stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[0923] In some embodiments, the mEVs are from bacteria of the class *Synergistia* [phylum *Synergistota*]. In some embodiments, the mEVs are from bacteria of the order *Synergistales*. In some embodiments, the mEVs are from bacteria of the family *Synergistaceae*. In some embodiments, the mEVs are from bacteria of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the mEVs are from bacteria of the class *Synergistia* that stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[0924] In some embodiments, the mEVs are from bacteria that produce metabolites, e.g., the bacteria produce butyrate, iosine, propionate, or tryptophan metabolites.

[0925] In some embodiments, the bacteria produce butyrate. In some embodiments, the bacteria are from the genus *Blautia*; *Christensella*; *Copracoccus*; *Eubacterium*; *Lachnospiraceae*; *Megasphaera*; or *Roseburia*.

[0926] In some embodiments, the bacteria produce iosine. In some embodiments, the bacteria are from the genus *Bifidobacterium*; *Lactobacillus*; or *Olsenella*.

[0927] In some embodiments, the bacteria produce propionate. In some embodiments, the bacteria are from the genus *Akkermansia*; *Bacteriodes*; *Dialister*; *Eubacterium*; *Megasphaera*; *Parabacteriodes*; *Prevotella*; *Ruminococcus*; or *Veillonella*.

[0928] In some embodiments, the bacteria produce tryptophan metabolites. In some embodiments, the bacteria are from the genus *Lactobacillus* or *Peptostreptococcus*.

[0929] In some embodiments, the mEVs are from bacteria that produce inhibitors of histone deacetylase 3 (HDAC3). In some embodiments, the bacteria are from the species *Bariatricus massiliensis*, *Faecalibacterium prausnitzii*, *Megasphaera massiliensis* or *Roseburia intestinalis*.

[0930] In some embodiments, the pharmaceutical agent comprises bacteria and the dose of bacteria is about 1×10^7 to about 2×10^{12} (e.g., about 3×10^{10} or about 1.5×10^{11} or about 1.5×10^{12}) cells (e.g., wherein cell number is determined by total cell count, which is determined by Coulter counter), wherein the dose is per tablet. In some embodiments, the pharmaceutical agent comprises bacteria and the dose of bacteria is about 1×10^{10} to about 2×10^{12} (e.g., about 1.6×10^{11} or about 8×10^{11} or about 9.6×10^{11} or about 12.8×10^{11} or about 1.6×10^{12}) cells (e.g., wherein cell number is determined by total cell count, which is determined by Coulter counter), wherein the dose is per tablet.

[0931] In some embodiments, the pharmaceutical agent comprises bacteria and the dose of bacteria is about 1×10^9 , about 3×10^9 , about 5×10^9 , about 1.5×10^{10} , about 3×10^{10} , about 5×10^{10} , about 1.5×10^{11} , about 1.5×10^{12} , or about 2×10^{12} cells, wherein the dose is per tablet.

[0932] In some embodiments, the pharmaceutical agent comprises mEVs and the dose of mEVs is about 1×10^5 to about 7×10^{13} particles (e.g., wherein particle count is determined by NTA (nanoparticle tracking analysis)), wherein the dose is per capsule or tablet or per total number of minitabets in a capsule. In some embodiments, the pharmaceutical agent comprises mEVs and the dose of mEVs is about 1×10^{10} to about 7×10^{13} particles (e.g., wherein particle count is determined by NTA (nanoparticle tracking analysis)), wherein the dose is per tablet.

[0933] In some embodiments, the pharmaceutical agent comprises bacteria and/or mEVs and the dose of pharmaceutical agent (e.g., bacteria and/or mEVs) is about 10 mg to about 3500 mg, wherein the dose is per tablet.

[0934] In some embodiments, the pharmaceutical agent comprises bacteria and/or mEVs and the dose of drug substance that contains the pharmaceutical agent (e.g., bacteria

and/or mEVs) is about 30 mg to about 1300 mg (by weight of bacteria and/or mEVs) (about 25, about 30, about 35, about 50, about 75, about 100, about 120, about 150, about 250, about 300, about 350, about 400, about 500, about 600, about 700, about 750, about 800, about 900, about 1000, about 1100, about 1200, about 1250, about 1300, about 2000, about 2500, about 3000, or about 3500 mg, wherein the dose is per tablet.

[0935] In some embodiments, the pharmaceutical agent comprises bacteria and/or mEVs and the dose of pharmaceutical agent (e.g., bacteria and/or mEVs) is about 2×10^6 to about 2×10^{16} particles (e.g., wherein particle count is determined by NTA (nanoparticle tracking analysis)), wherein the dose is per tablet.

[0936] In some embodiments, the pharmaceutical agent comprises bacteria and/or mEVs and the dose of pharmaceutical agent (e.g., bacteria and/or mEVs) is about 5 mg to about 900 mg total protein (e.g., wherein total protein is determined by Bradford assay or BCA), wherein the dose is per tablet.

[0937] In some embodiments, the can be (or be present in) a medicinal product, medical food, a food product, or a dietary supplement.

[0938] In some embodiments, the solid dosage form further comprises one or more additional pharmaceutical agents.

In some embodiments, the solid dosage form further comprises an excipient (e.g., an excipient described herein, e.g., a diluent, a binder and/or an adhesive, a disintegrant, a lubricant and/or a glidant, a coloring agent, a flavoring agent, and/or a sweetening agent).

[0939] In some aspects, the disclosure provides a method for preparing an enterically coated minitabiet comprising a pharmaceutical agent (e.g., a therapeutically effective amount thereof), wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), the method comprising:

[0940] a) combining the pharmaceutical agent with a pharmaceutically acceptable excipient;

[0941] b) compressing the pharmaceutical agent and pharmaceutically acceptable excipient, thereby forming a minitabiet; and

[0942] c) enterically coating the minitabiet, thereby preparing the enterically coated minitabiet.

[0943] In some embodiments, one or more minitabiets are loaded into a capsule. In some embodiments, the method further comprises banding the capsule after loading the

capsule. In some embodiments, the capsule is banded with an HPMC-based banding solution.

[0944] In some embodiments, the minitabket (e.g., enterically coated minitabket) is a 1mm minitabket, 1.5 mm minitabket, 2mm minitabket, 3mm minitabket, or 4mm minitabket. In some embodiments, a plurality of enterically coated minitabkets are contained in a capsule (e.g., a size 0 capsule can contain about 31 to about 35 (e.g., 33) minitabkets, wherein the minitabkets are 3mm in size). In some embodiments, the capsule is a size 00, size 0, size 1, size 2, size 3, size 4, or size 5 capsule. In some embodiments, the capsule comprises HPMC (hydroxyl propyl methyl cellulose) or gelatin.

[0945] In some embodiments, the enteric coating comprises one enteric coating.

[0946] In some embodiments, the enteric coating comprises an inner enteric coating and an outer enteric coating, and wherein the inner and outer enteric coatings are not identical (e.g., the inner and outer enteric coatings do not contain identical components in identical amounts).

[0947] In some embodiments, the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) comprises a polymethacrylate-based copolymer.

[0948] In some embodiments, the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) comprises a methacrylic acid ethyl acrylate (MAE) copolymer (1:1).

[0949] In some embodiments, the one enteric coating comprises methacrylic acid ethyl acrylate (MAE) copolymer (1:1) (such as Kollicoat MAE 100P).

[0950] In some embodiments, the one enteric coating comprises a Eudragit copolymer, e.g., a Eudragit L (e.g., Eudragit L 100-55; Eudragit L 30 D-55), a Eudragit S, a Eudragit RL, a Eudragit RS, a Eudragit E, or a Eudragit FS (e.g., Eudragit FS 30 D).

[0951] In some embodiments, the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) comprises cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), poly(vinyl acetate phthalate) (PVAP), hydroxypropyl methylcellulose phthalate (HPMCP), a fatty acid, a wax, shellac (esters of aleurtic acid), a plastic, a plant fiber, zein, Aqua-Zein (an aqueous zein formulation containing no alcohol), amylose starch, a starch derivative, a dextrin, a methyl acrylate-methacrylic acid copolymer, cellulose acetate succinate, hydroxypropyl methyl cellulose

acetate succinate (hypromellose acetate succinate), a methyl methacrylate-methacrylic acid copolymer, or sodium alginate.

[0952] In some embodiments, the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) comprises an anionic polymeric material.

[0953] In some embodiments, the pharmaceutical agent comprises bacteria.

[0954] In some embodiments, the pharmaceutical agent comprises microbial extracellular vesicles (mEV).

[0955] In some embodiments, the pharmaceutical agent comprises bacteria and microbial extracellular vesicles (mEV).

[0956] In some embodiments, the pharmaceutical agent has one or more beneficial immune effects outside the gastrointestinal tract, e.g., when the solid dosage form is orally administered.

[0957] In some embodiments, the pharmaceutical agent modulates immune effects outside the gastrointestinal tract (e.g., outside of the small intestine) in the subject, e.g., when the solid dosage form is orally administered.

[0958] In some embodiments, the pharmaceutical agent causes a systemic effect (e.g., an effect outside of the gastrointestinal tract), e.g., when the solid dosage form is orally administered.

[0959] In some embodiments, the pharmaceutical agent acts on immune cells and/or epithelial cells in the small intestine (e.g., causing a systemic effect (e.g., an effect outside of the gastrointestinal tract), e.g., when the solid dosage form is orally administered.

[0960] In some embodiments, the pharmaceutical agent comprises isolated bacteria (e.g., from one or more strains of bacteria (e.g., bacteria of interest) (e.g., a therapeutically effective amount thereof)). E.g., wherein at least 50%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% of the content of the pharmaceutical agent is the isolated bacteria (e.g., bacteria of interest).

[0961] In some embodiments, the pharmaceutical agent comprises bacteria that have been gamma irradiated, UV irradiated, heat inactivated, acid treated, or oxygen sparged.

[0962] In some embodiments, the pharmaceutical agent comprises live bacteria.

[0963] In some embodiments, the pharmaceutical agent comprises dead bacteria.

- [0964] In some embodiments, the pharmaceutical agent comprises non-replicating bacteria.
- [0965] In some embodiments, the pharmaceutical agent comprises bacteria from one strain of microbe (e.g., bacteria).
- [0966] In some embodiments, the bacteria are lyophilized (e.g., the lyophilized product further comprises a pharmaceutically acceptable excipient) (e.g., a powder form).
- [0967] In some embodiments, the bacteria are gamma irradiated.
- [0968] In some embodiments, the bacteria are UV irradiated.
- [0969] In some embodiments, the bacteria are heat inactivated (e.g., at 50°C for two hours or at 90°C for two hours).
- [0970] In some embodiments, the bacteria are acid treated.
- [0971] In some embodiments, the bacteria are oxygen sparged (e.g., at 0.1 vvm for two hours).
- [0972] In some embodiments, the bacteria are Gram positive bacteria.
- [0973] In some embodiments, the bacteria are Gram negative bacteria.
- [0974] In some embodiments, the bacteria are aerobic bacteria.
- [0975] In some embodiments, the bacteria are anaerobic bacteria. In some embodiments, the anaerobic bacteria comprise obligate anaerobes. In some embodiments, the anaerobic bacteria comprise facultative anaerobes.
- [0976] In some embodiments, the bacteria are acidophile bacteria.
- [0977] In some embodiments, the bacteria are alkaliphile bacteria.
- [0978] In some embodiments, the bacteria are neutralophile bacteria.
- [0979] In some embodiments, the bacteria are fastidious bacteria.
- [0980] In some embodiments, the bacteria are nonfastidious bacteria.
- [0981] In some embodiments, the bacteria are of a taxonomic group (e.g., class, order, family, genus, species or strain) listed in Table 1, Table 2, or Table 3.
- [0982] In some embodiments, the bacteria are a bacterial strain listed in Table 1, Table 2, or Table 3.
- [0983] In some embodiments, the bacteria are of a taxonomic group (e.g., class, order, family, genus, species or strain) listed in Table J.
- [0984] In some embodiments, the bacteria are a bacterial strain listed in Table J.
- [0985] In some embodiments, the Gram negative bacteria belong to class *Negativicutes*.

[0986] In some embodiments, the Gram negative bacteria belong to family *Veillonellaceae*, *Selenomonadaceae*, *Acidaminococcaceae*, or *Sporomusaceae*.

[0987] In some embodiments, the bacteria of the genus *Megasphaera*, *Selenomonas*, *Propionospora*, or *Acidaminococcus*.

[0988] In some embodiments, the bacteria are *Megasphaera* sp., *Selenomonas felix*, *Acidaminococcus intestine*, or *Propionospora* sp. bacteria.

[0989] In some embodiments, the bacteria are of the genus *Lactococcus*, *Prevotella*, *Bifidobacterium*, or *Veillonella*.

[0990] In some embodiments, the bacteria are *Lactococcus lactis cremoris* bacteria.

[0991] In some embodiments, the bacteria are *Prevotella histicola* bacteria.

[0992] In some embodiments, the bacteria are *Bifidobacterium animalis* bacteria.

[0993] In some embodiments, the bacteria are *Veillonella parvula* bacteria.

[0994] In some embodiments, the bacteria are *Lactococcus lactis cremoris* bacteria.

In some embodiments, the *Lactococcus lactis cremoris* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the *Lactococcus* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the *Lactococcus* bacteria are *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368).

[0995] In some embodiments, the bacteria are *Prevotella* bacteria. In some embodiments, the *Prevotella* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Prevotella* Strain B 50329 (NRRL accession number B 50329). In some embodiments, the *Prevotella* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Prevotella* Strain B 50329 (NRRL accession number B 50329). In some embodiments, the *Prevotella* bacteria are *Prevotella* Strain B 50329 (NRRL accession number B 50329).

[0996] In some embodiments, the bacteria are *Bifidobacterium* bacteria. In some embodiments, the *Bifidobacterium* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097. In some

embodiments, the *Bifidobacterium* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097. In some embodiments, the *Bifidobacterium* bacteria are *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097.

[0997] In some embodiments, the bacteria are *Veillonella* bacteria. In some embodiments, the *Veillonella* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the *Veillonella* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the *Veillonella* bacteria are *Veillonella* bacteria deposited as ATCC designation number PTA-125691.

[0998] In some embodiments, the bacteria are from *Ruminococcus gnavus* bacteria. In some embodiments, the *Ruminococcus gnavus* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695.

[0999] In some embodiments, the bacteria are *Megasphaera sp.* bacteria. In some embodiments, the *Megasphaera sp.* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some embodiments, the *Megasphaera sp.* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some embodiments, the *Megasphaera sp.* bacteria are *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770.

[1000] In some embodiments, the bacteria are *Fournierella massiliensis* bacteria. In some embodiments, the *Fournierella massiliensis* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696.

[1001] In some embodiments, the bacteria are *Harryflintia acetispora* bacteria. In some embodiments, the *Harryflintia acetispora* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694.

[1002] In some embodiments, the bacteria are of the family *Acidaminococcaceae*, *Alcaligenaceae*, *Akkermansiaceae*, *Bacteriodaceae*, *Bifidobacteriaceae*, *Burkholderiaceae*, *Catabacteriaceae*, *Clostridiaceae*, *Coriobacteriaceae*, *Enterobacteriaceae*, *Enterococcaceae*, *Fusobacteriaceae*, *Lachnospiraceae*, *Listeraceae*, *Mycobacteriaceae*, *Neisseriaceae*, *Odoribacteraceae*, *Oscillospiraceae*, *Peptococcaceae*, *Peptostreptococcaceae*, *Porphyromonadaceae*, *Prevotellaceae*, *Propionibacteraceae*, *Rikenellaceae*, *Ruminococcaceae*, *Selenomonadaceae*, *Sporomusaceae*, *Streptococcaceae*, *Streptomyetaceae*, *Sutterellaceae*, *Synergistaceae*, or *Veillonellaceae*.

[1003] In some embodiments, the bacteria are of the genus *Akkermansia*, *Christensenella*, *Blautia*, *Enterococcus*, *Eubacterium*, *Roseburia*, *Bacteroides*, *Parabacteroides*, or *Erysipelatoclostridium*.

[1004] In some embodiments, the bacteria are *Blautia hydrogenotrophica*, *Blautia stercoris*, *Blautia wexlerae*, *Eubacterium faecium*, *Eubacterium contortum*, *Eubacterium rectale*, *Enterococcus faecalis*, *Enterococcus durans*, *Enterococcus villorum*, *Enterococcus*

gallinarum; *Bifidobacterium lactis*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, *Bifidobacterium animalis*, or *Bifidobacterium breve* bacteria.

[1005] In some embodiments, the bacteria are *BCG (bacillus Calmette-Guerin)*, *Parabacteroides*, *Blautia*, *Veillonella*, *Lactobacillus salivarius*, *Agathobaculum*, *Ruminococcus gnavus*, *Paraclostridium benzoelyticum*, *Turicibacter sanguinus*, *Burkholderia*, *Klebsiella quasipneumoniae ssp similpneumoniae*, *Klebsiella oxytoca*, *Tyzzera nexilis*, or *Neisseria* bacteria.

[1006] In some embodiments, the bacteria are *Blautia hydrogenotrophica* bacteria.

[1007] In some embodiments, the bacteria are *Blautia stercoris* bacteria.

[1008] In some embodiments, the bacteria are *Blautia wexlerae* bacteria.

[1009] In some embodiments, the bacteria are *Enterococcus gallinarum* bacteria.

[1010] In some embodiments, the bacteria are *Enterococcus faecium* bacteria.

[1011] In some embodiments, the bacteria are *Bifidobacterium bifidum* bacteria.

[1012] In some embodiments, the bacteria are *Bifidobacterium breve* bacteria.

[1013] In some embodiments, the bacteria are *Bifidobacterium longum* bacteria.

[1014] In some embodiments, the bacteria are *Roseburia hominis* bacteria.

[1015] In some embodiments, the bacteria are *Bacteroides thetaiotaomicron* bacteria.

[1016] In some embodiments, the bacteria are *Bacteroides coprocola* bacteria.

[1017] In some embodiments, the bacteria are *Erysipelatoclostridium ramosum* bacteria.

[1018] In some embodiments, the bacteria are *Megasphaera massiliensis* bacteria.

[1019] In some embodiments, the bacteria are *Eubacterium* bacteria.

[1020] In some embodiments, the bacteria are *Parabacteroides distasonis* bacteria.

[1021] In some embodiments, the bacteria are *Lactobacillus plantarum* bacteria.

[1022] In some embodiments, the bacteria are bacteria of the *Negativicutes* class.

[1023] In some embodiments, the bacteria are of the *Veillonellaceae* family.

[1024] In some embodiments, the bacteria are of the *Selenomonadaceae* family.

[1025] In some embodiments, the bacteria are of the *Acidaminococcaceae* family.

[1026] In some embodiments, the bacteria are of the *Sporomusaceae* family.

[1027] In some embodiments, the bacteria are of the *Megasphaera* genus.

[1028] In some embodiments, the bacteria are of the *Selenomonas* genus.

[1029] In some embodiments, the bacteria are of the *Propionospora* genus.

- [1030] In some embodiments, the bacteria are of the *Acidaminococcus* genus.
- [1031] In some embodiments, the bacteria are *Megasphaera sp.* bacteria.
- [1032] In some embodiments, the bacteria are *Selenomonas felix* bacteria.
- [1033] In some embodiments, the bacteria are *Acidaminococcus intestini* bacteria.
- [1034] In some embodiments, the bacteria are *Propionospora sp.* bacteria.
- [1035] In some embodiments, the bacteria are bacteria of the *Clostridia* class.
- [1036] In some embodiments, the bacteria are of the *Oscillospiraceae* family.
- [1037] In some embodiments, the bacteria are of the *Faecalibacterium* genus.
- [1038] In some embodiments, the bacteria are of the *Fournierella* genus.
- [1039] In some embodiments, the bacteria are of the *Harryflintia* genus.
- [1040] In some embodiments, the bacteria are of the *Agathobaculum* genus.
- [1041] In some embodiments, the bacteria are *Faecalibacterium prausnitzii* (e.g., *Faecalibacterium prausnitzii* Strain A) bacteria.
- [1042] In some embodiments, the bacteria are *Fournierella massiliensis* (e.g., *Fournierella massiliensis* Strain A) bacteria.
- [1043] In some embodiments, the bacteria are *Harryflintia acetispora* (e.g., *Harryflintia acetispora* Strain A) bacteria.
- [1044] In some embodiments, the bacteria are *Agathobaculum sp.* (e.g., *Agathobaculum sp.* Strain A) bacteria.
- [1045] In some embodiments, the bacteria are a strain of *Agathobaculum sp.* In some embodiments, the *Agathobaculum sp.* strain is a strain comprising at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity (e.g., at least 99.5% sequence identity, at least 99.6% sequence identity, at least 99.7% sequence identity, at least 99.8% sequence identity, at least 99.9% sequence identity) to the nucleotide sequence (e.g., genomic sequence, 16S sequence, CRISPR sequence) of the *Agathobaculum sp.* Strain A (ATCC Deposit Number PTA-125892). In some embodiments, the *Agathobaculum sp.* strain is the *Agathobaculum sp.* Strain A (ATCC Deposit Number PTA-125892).
- [1046] In some embodiments, the bacteria are of the class *Bacteroidia* [phylum *Bacteroidota*]. In some embodiments, the bacteria are of order *Bacteroidales*. In some embodiments, the bacteria are of the family *Porphyromonadaceae*. In some embodiments, the bacteria are of the family *Prevotellaceae*. In some embodiments, the bacteria are of the class *Bacteroidia* wherein the cell envelope structure of the bacteria is diderm. In some

embodiments, the bacteria are of the class *Bacteroidia* that stain Gram negative. In some embodiments, the bacteria are of the class *Bacteroidia* wherein the bacteria is diderm and the bacteria stain Gram negative.

[1047] In some embodiments, the bacteria are of the class *Clostridia* [phylum *Firmicutes*]. In some embodiments, the bacteria are of the order *Eubacteriales*. In some embodiments, the bacteria are of the family *Oscillispiraceae*. In some embodiments, the bacteria are of the family *Lachnospiraceae*. In some embodiments, the bacteria are of the family *Peptostreptococcaceae*. In some embodiments, the bacteria are of the family *Clostridiales* family XIII/ *Incertae sedis* 41. In some embodiments, the bacteria are of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm. In some embodiments, the bacteria are of the class *Clostridia* that stain Gram negative. In some embodiments, the bacteria are of the class *Clostridia* that stain Gram positive. In some embodiments, the bacteria are of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram negative. In some embodiments, the bacteria are of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram positive.

[1048] In some embodiments, the bacteria are of the class *Negativicutes* [phylum *Firmicutes*]. In some embodiments, the bacteria are of the order *Veillonellales*. In some embodiments, the bacteria are of the family *Veillonelloceae*. In some embodiments, the bacteria are of the order *Selenomonadales*. In some embodiments, the bacteria are of the family *Selenomonadaceae*. In some embodiments, the bacteria are of the family *Sporomusaceae*. In some embodiments, the bacteria are of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the bacteria are of the class *Negativicutes* that stain Gram negative. In some embodiments, the bacteria are of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[1049] In some embodiments, the bacteria are of the class *Synergistia* [phylum *Synergistota*]. In some embodiments, the bacteria are of the order *Synergistales*. In some embodiments, the bacteria are of the family *Synergistaceae*. In some embodiments, the bacteria are of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the bacteria are of the class *Synergistia* that stain Gram negative. In some embodiments, the bacteria are of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[1050] In some embodiments, the bacteria are bacteria that produce metabolites, e.g., the bacteria produce butyrate, irosine, propionate, or tryptophan metabolites.

[1051] In some embodiments, the bacteria produce butyrate. In some embodiments, the bacteria are from the genus *Blautia*; *Christensenella*; *Copracoccus*; *Eubacterium*; *Lachnospiraceae*; *Megasphaera*; or *Roseburia*.

[1052] In some embodiments, the bacteria produce irosine. In some embodiments, the bacteria are from the genus *Bifidobacterium*; *Lactobacillus*; or *Olsenella*.

[1053] In some embodiments, the bacteria produce propionate. In some embodiments, the bacteria are from the genus *Akkermansia*; *Bacteriodes*; *Dialister*; *Eubacterium*; *Megasphaera*; *Parabacteriodes*; *Prevotella*; *Ruminococcus*; or *Veillonella*.

[1054] In some embodiments, the bacteria produce tryptophan metabolites. In some embodiments, the bacteria are from the genus *Lactobacillus* or *Peptostreptococcus*.

[1055] In some embodiments, the bacteria are bacteria that produce inhibitors of histone deacetylase 3 (HDAC3). In some embodiments, the bacteria are from the species *Bariatricus massiliensis*, *Faecalibacterium prausnitzii*, *Megasphaera massiliensis* or *Roseburia intestinalis*.

[1056] In some embodiments, the pharmaceutical agent comprises isolated mEVs (e.g., from one or more strains of bacteria (e.g., bacteria of interest)) (e.g., a therapeutically effective amount thereof). E.g., wherein at least 50%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% of the content of the pharmaceutical agent is isolated mEV of bacteria (e.g., bacteria of interest).

[1057] In some embodiments, the pharmaceutical agent comprises mEVs and the mEVs comprise secreted mEVs (smEVs).

[1058] In some embodiments, the pharmaceutical agent comprises mEVs and the mEVs comprise processed mEVs (pmEVs).

[1059] In some embodiments, the pharmaceutical agent comprises pmEVs and the pmEVs are produced from bacteria that have been gamma irradiated, UV irradiated, heat inactivated, acid treated, or oxygen sparged.

[1060] In some embodiments, the pharmaceutical agent comprises pmEVs and the pmEVs are produced from live bacteria.

[1061] In some embodiments, the pharmaceutical agent comprises pmEVs and the pmEVs are produced from dead bacteria.

- [1062] In some embodiments, the pharmaceutical agent comprises pmEVs and the pmEVs are produced from non-replicating bacteria.
- [1063] In some embodiments, the pharmaceutical agent comprises mEVs and the mEVs are from one strain of bacteria.
- [1064] In some embodiments, the mEVs are lyophilized (e.g., the lyophilized product further comprises a pharmaceutically acceptable excipient).
- [1065] In some embodiments, the mEVs are gamma irradiated.
- [1066] In some embodiments, the mEVs are UV irradiated.
- [1067] In some embodiments, the mEVs are heat inactivated (e.g., at 50°C for two hours or at 90°C for two hours).
- [1068] In some embodiments, the mEVs are acid treated.
- [1069] In some embodiments, the mEVs are oxygen sparged (e.g., at 0.1 vvm for two hours).
- [1070] In some embodiments, the mEVs are from Gram positive bacteria.
- [1071] In some embodiments, the mEVs are from Gram negative bacteria.
- [1072] In some embodiments, the mEVs are from aerobic bacteria.
- [1073] In some embodiments, the mEVs are from anaerobic bacteria. In some embodiments, the anaerobic bacteria comprise obligate anaerobes. In some embodiments, the anaerobic bacteria comprise facultative anaerobes.
- [1074] In some embodiments, the mEVs are from acidophile bacteria.
- [1075] In some embodiments, the mEVs are from alkaliphile bacteria.
- [1076] In some embodiments, the mEVs are from neutralophile bacteria.
- [1077] In some embodiments, the mEVs are from fastidious bacteria.
- [1078] In some embodiments, the mEVs are from nonfastidious bacteria.
- [1079] In some embodiments, the mEVs are from bacteria of a taxonomic group (e.g., class, order, family, genus, species or strain) listed in Table 1, Table 2, or Table 3.
- [1080] In some embodiments, the mEVs are from a bacterial strain listed in Table 1, Table 2, or Table 3.
- [1081] In some embodiments, the mEVs are from bacteria of a taxonomic group (e.g., class, order, family, genus, species or strain) listed in Table J.
- [1082] In some embodiments, the mEVs are from a bacterial strain listed in Table J.
- [1083] In some embodiments, the Gram negative bacteria belong to class *Negativicutes*.

- [1084] In some embodiments, the Gram negative bacteria belong to family *Veillonellaceae*, *Selenomonadaceae*, *Acidaminococcaceae*, or *Sporomusaceae*.
- [1085] In some embodiments, the mEVs are from bacteria of the genus *Megasphaera*, *Selenomonas*, *Propionospora*, or *Acidaminococcus*.
- [1086] In some embodiments, the mEVs are *Megasphaera sp.*, *Selenomonas felix*, *Acidaminococcus intestine*, or *Propionospora sp.* bacteria.
- [1087] In some embodiments, the mEVs are from bacteria of the genus *Lactococcus*, *Prevotella*, *Bifidobacterium*, or *Veillonella*.
- [1088] In some embodiments, the mEVs are from *Lactococcus lactis cremoris* bacteria.
- [1089] In some embodiments, the mEVs are from *Prevotella histicola* bacteria.
- [1090] In some embodiments, the mEVs are from *Bifidobacterium animalis* bacteria.
- [1091] In some embodiments, the mEVs are from *Veillonella parvula* bacteria.
- [1092] In some embodiments, the mEVs are from *Lactococcus lactis cremoris* bacteria. In some embodiments, the *Lactococcus lactis cremoris* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the *Lactococcus* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the *Lactococcus* bacteria are from *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368).
- [1093] In some embodiments, the mEVs are from *Prevotella* bacteria. In some embodiments, the *Prevotella* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Prevotella* Strain B 50329 (NRRL accession number B 50329). In some embodiments, the *Prevotella* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Prevotella* Strain B 50329 (NRRL accession number B 50329). In some embodiments, the *Prevotella* bacteria are from *Prevotella* Strain B 50329 (NRRL accession number B 50329).
- [1094] In some embodiments, the mEVs are from *Bifidobacterium* bacteria. In some embodiments, the *Bifidobacterium* bacteria are from a strain comprising at least 90% (or at

least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097. In some embodiments, the *Bifidobacterium* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097. In some embodiments, the *Bifidobacterium* bacteria are from *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097.

[1095] In some embodiments, the mEVs are from *Veillonella* bacteria. In some embodiments, the *Veillonella* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the *Veillonella* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the *Veillonella* bacteria are from *Veillonella* bacteria deposited as ATCC designation number PTA-125691.

[1096] In some embodiments, the mEVs are from *Ruminococcus gnavus* bacteria. In some embodiments, the *Ruminococcus gnavus* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are from *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695.

[1097] In some embodiments, the mEVs are from *Megasphaera sp.* bacteria. In some embodiments, the *Megasphaera sp.* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some embodiments, the *Megasphaera sp.* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In

some embodiments, the *Megasphaera sp.* bacteria are from *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770.

[1098] In some embodiments, the mEVs are from *Fournierella massiliensis* bacteria. In some embodiments, the *Fournierella massiliensis* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are from *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696.

[1099] In some embodiments, the mEVs are from *Harryflintia acetispora* bacteria. In some embodiments, the *Harryflintia acetispora* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are from *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694.

[1100] In some embodiments, the mEVs are from bacteria of the family *Acidaminococcaceae*, *Alcaligenaceae*, *Akkermansiaceae*, *Bacteriodaceae*, *Bifidobacteriaceae*, *Burkholderiaceae*, *Catabacteriaceae*, *Clostridiaceae*, *Coriobacteriaceae*, *Enterobacteriaceae*, *Enterococcaceae*, *Fusobacteriaceae*, *Lachnospiraceae*, *Listeraceae*, *Mycobacteriaceae*, *Neisseriaceae*, *Odoribacteraceae*, *Oscillospiraceae*, *Peptococcaceae*, *Peptostreptococcaceae*, *Porphyromonadaceae*, *Prevotellaceae*, *Propionibacteraceae*, *Rikenellaceae*, *Ruminococcaceae*, *Selenomonadaceae*, *Sporomusaceae*, *Streptococcaceae*, *Streptomyetaceae*, *Sutterellaceae*, *Synergistaceae*, or *Veillonellaceae*.

[1101] In some embodiments, the mEVs are from bacteria of the genus *Akkermansia*, *Christensenella*, *Blautia*, *Enterococcus*, *Eubacterium*, *Roseburia*, *Bacteroides*, *Parabacteroides*, or *Erysipelatoclostridium*.

- [1102] In some embodiments, the mEVs are from *Blautia hydrogenotrophica*, *Blautia stercoris*, *Blautia wexlerae*, *Eubacterium faecium*, *Eubacterium contortum*, *Eubacterium rectale*, *Enterococcus faecalis*, *Enterococcus durans*, *Enterococcus villorum*, *Enterococcus gallinarum*; *Bifidobacterium lactis*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, *Bifidobacterium animalis*, or *Bifidobacterium breve* bacteria.
- [1103] In some embodiments, the mEVs are from *BCG (bacillus Calmette-Guerin)*, *Parabacteroides*, *Blautia*, *Veillonella*, *Lactobacillus salivarius*, *Agathobaculum*, *Ruminococcus gnavus*, *Paraclostridium benzoelyticum*, *Turicibacter sanguinus*, *Burkholderia*, *Klebsiella quasipneumoniae ssp similpneumoniae*, *Klebsiella oxytoca*, *Tyzzerelex nexilis*, or *Neisseria* bacteria.
- [1104] In some embodiments, the mEVs are from *Blautia hydrogenotrophica* bacteria.
- [1105] In some embodiments, the mEVs are from *Blautia stercoris* bacteria.
- [1106] In some embodiments, the mEVs are from *Blautia wexlerae* bacteria.
- [1107] In some embodiments, the mEVs are from *Enterococcus gallinarum* bacteria.
- [1108] In some embodiments, the mEVs are from *Enterococcus faecium* bacteria.
- [1109] In some embodiments, the mEVs are from *Bifidobacterium bifidum* bacteria.
- [1110] In some embodiments, the mEVs are from *Bifidobacterium breve* bacteria.
- [1111] In some embodiments, the mEVs are from *Bifidobacterium longum* bacteria.
- [1112] In some embodiments, the mEVs are from *Roseburia hominis* bacteria.
- [1113] In some embodiments, the mEVs are from *Bacteroides thetaiotaomicron* bacteria.
- [1114] In some embodiments, the mEVs are from *Bacteroides coprocola* bacteria.
- [1115] In some embodiments, the mEVs are from *Erysipelatoclostridium ramosum* bacteria.
- [1116] In some embodiments, the mEVs are from *Megasphaera massiliensis* bacteria.
- [1117] In some embodiments, the mEVs are from *Eubacterium* bacteria.
- [1118] In some embodiments, the mEVs are from *Parabacteroides distasonis* bacteria.
- [1119] In some embodiments, the mEVs are from *Lactobacillus plantarum* bacteria.

- [1120] In some embodiments, the mEVs are from bacteria of the *Negativicutes* class.
- [1121] In some embodiments, the mEVs are from bacteria of the *Veillonellaceae* family.
- [1122] In some embodiments, the mEVs are from bacteria of the *Selenomonadaceae* family.
- [1123] In some embodiments, the mEVs are from bacteria of the *Acidaminococcaceae* family.
- [1124] In some embodiments, the mEVs are from bacteria of the *Sporomusaceae* family.
- [1125] In some embodiments, the mEVs are from bacteria of the *Megasphaera* genus.
- [1126] In some embodiments, the mEVs are from bacteria of the *Selenomonas* genus.
- [1127] In some embodiments, the mEVs are from bacteria of the *Propionospora* genus.
- [1128] In some embodiments, the mEVs are from bacteria of the *Acidaminococcus* genus.
- [1129] In some embodiments, the mEVs are from *Megasphaera sp.* bacteria.
- [1130] In some embodiments, the mEVs are from *Selenomonas felix* bacteria.
- [1131] In some embodiments, the mEVs are from *Acidaminococcus intestini* bacteria.
- [1132] In some embodiments, the mEVs are from *Propionospora sp.* bacteria.
- [1133] In some embodiments, the mEVs are from bacteria of the *Clostridia* class.
- [1134] In some embodiments, the mEVs are from bacteria of the *Oscillospiraceae* family.
- [1135] In some embodiments, the mEVs are from bacteria of the *Faecalibacterium* genus.
- [1136] In some embodiments, the mEVs are from bacteria of the *Fournierella* genus.
- [1137] In some embodiments, the mEVs are from bacteria of the *Harryflintia* genus.
- [1138] In some embodiments, the mEVs are from bacteria of the *Agathobaculum* genus.

[1139] In some embodiments, the mEVs are from *Faecalibacterium prausnitzii* (e.g., *Faecalibacterium prausnitzii* Strain A) bacteria.

[1140] In some embodiments, the mEVs are from *Fournierella massiliensis* (e.g., *Fournierella massiliensis* Strain A) bacteria.

[1141] In some embodiments, the mEVs are from *Harryflintia acetispora* (e.g., *Harryflintia acetispora* Strain A) bacteria.

[1142] In some embodiments, the mEVs are from *Agathobaculum sp.* (e.g., *Agathobaculum sp.* Strain A) bacteria.

[1143] In some embodiments, the mEVs are from a strain of *Agathobaculum sp.* In some embodiments, the *Agathobaculum sp.* strain is a strain comprising at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity (e.g., at least 99.5% sequence identity, at least 99.6% sequence identity, at least 99.7% sequence identity, at least 99.8% sequence identity, at least 99.9% sequence identity) to the nucleotide sequence (e.g., genomic sequence, 16S sequence, CRISPR sequence) of the *Agathobaculum sp.* Strain A (ATCC Deposit Number PTA-125892). In some embodiments, the *Agathobaculum sp.* strain is the *Agathobaculum sp.* Strain A (ATCC Deposit Number PTA-125892).

[1144] In some embodiments, the mEVs are from bacteria of the class *Bacteroidia* [phylum *Bacteroidota*]. In some embodiments, the mEVs are from bacteria of order *Bacteroidales*. In some embodiments, the mEVs are from bacteria of the family *Porphyromonadaceae*. In some embodiments, the mEVs are from bacteria of the family *Prevotellaceae*. In some embodiments, the mEVs are from bacteria of the class *Bacteroidia* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the mEVs are from bacteria of the class *Bacteroidia* that stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Bacteroidia* wherein the bacteria is diderm and the bacteria stain Gram negative.

[1145] In some embodiments, the mEVs are from bacteria of the class *Clostridia* [phylum *Firmicutes*]. In some embodiments, the mEVs are from bacteria of the order *Eubacteriales*. In some embodiments, the mEVs are from bacteria of the family *Oscillispiraceae*. In some embodiments, the mEVs are from bacteria of the family *Lachnospiraceae*. In some embodiments, the mEVs are from bacteria of the family *Peptostreptococcaceae*. In some embodiments, the mEVs are from bacteria of the family *Clostridiales family XIII/ Incertae sedis 41*. In some embodiments, the mEVs are from

bacteria of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm. In some embodiments, the mEVs are from bacteria of the class *Clostridia* that stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Clostridia* that stain Gram positive. In some embodiments, the mEVs are from bacteria of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram positive.

[1146] In some embodiments, the mEVs are from bacteria of the class *Negativicutes* [phylum *Firmicutes*]. In some embodiments, the mEVs are from bacteria of the order *Veillonellales*. In some embodiments, the mEVs are from bacteria of the family *Veillonelloceae*. In some embodiments, the mEVs are from bacteria of the order *Selenomonadales*. In some embodiments, the mEVs are from bacteria of the family *Selenomonadaceae*. In some embodiments, the mEVs are from bacteria of the family *Sporomusaceae*. In some embodiments, the mEVs are from bacteria of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the mEVs are from bacteria of the class *Negativicutes* that stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[1147] In some embodiments, the mEVs are from bacteria of the class *Synergistia* [phylum *Synergistota*]. In some embodiments, the mEVs are from bacteria of the order *Synergistales*. In some embodiments, the mEVs are from bacteria of the family *Synergistaceae*. In some embodiments, the mEVs are from bacteria of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the mEVs are from bacteria of the class *Synergistia* that stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[1148] In some embodiments, the mEVs are from bacteria that produce metabolites, e.g., the bacteria produce butyrate, ioline, propionate, or tryptophan metabolites.

[1149] In some embodiments, the bacteria produce butyrate. In some embodiments, the bacteria are from the genus *Blautia*; *Christensella*; *Copracoccus*; *Eubacterium*; *Lachnospiraceae*; *Megasphaera*; or *Roseburia*.

[1150] In some embodiments, the bacteria produce irosine. In some embodiments, the bacteria are from the genus *Bifidobacterium*; *Lactobacillus*; or *Olsenella*.

[1151] In some embodiments, the bacteria produce propionate. In some embodiments, the bacteria are from the genus *Akkermansia*; *Bacteriodes*; *Dialister*; *Eubacterium*; *Megasphaera*; *Parabacteriodes*; *Prevotella*; *Ruminococcus*; or *Veillonella*.

[1152] In some embodiments, the bacteria produce tryptophan metabolites. In some embodiments, the bacteria are from the genus *Lactobacillus* or *Peptostreptococcus*.

[1153] In some embodiments, the mEVs are from bacteria that produce inhibitors of histone deacetylase 3 (HDAC3). In some embodiments, the bacteria are from the species *Bariatricus massiliensis*, *Faecalibacterium prausnitzii*, *Megasphaera massiliensis* or *Roseburia intestinalis*.

[1154] In some embodiments, the pharmaceutical agent comprises bacteria and the dose of bacteria is about 1×10^7 to about 2×10^{12} (e.g., about 3×10^{10} or about 1.5×10^{11} or about 1.5×10^{12}) cells (e.g., wherein cell number is determined by total cell count, which is determined by Coulter counter), wherein the dose is per capsule or per total number of minitabets in a capsule. In some embodiments, the pharmaceutical agent comprises bacteria and the dose of bacteria is about 1×10^{10} to about 2×10^{12} (e.g., about 1.6×10^{11} or about 8×10^{11} or about 9.6×10^{11} or about 12.8×10^{11} or about 1.6×10^{12}) cells (e.g., wherein cell number is determined by total cell count, which is determined by Coulter counter), wherein the dose is per capsule or per total number of minitabets in a capsule.

[1155] In some embodiments, the pharmaceutical agent comprises bacteria and the dose of bacteria is about 1×10^9 , about 3×10^9 , about 5×10^9 , about 1.5×10^{10} , about 3×10^{10} , about 5×10^{10} , about 1.5×10^{11} , about 1.5×10^{12} , or about 2×10^{12} cells, wherein the dose is per capsule or per total number of minitabets in a capsule.

[1156] In some embodiments, the pharmaceutical agent comprises mEVs and the dose of mEVs is about 1×10^5 to about 7×10^{13} particles (e.g., wherein particle count is determined by NTA (nanoparticle tracking analysis)), wherein the dose is per capsule or tablet or per total number of minitabets in a capsule. In some embodiments, the pharmaceutical agent comprises mEVs and the dose of mEVs is about 1×10^{10} to about 7×10^{13} particles (e.g., wherein particle count is determined by NTA (nanoparticle tracking analysis)), wherein the dose is per capsule or per total number of minitabets in a capsule.

[1157] In some embodiments, the pharmaceutical agent comprises bacteria and/or mEVs and the dose of the pharmaceutical agent (e.g., bacteria and/or mEVs) is about 10 mg

to about 3500 mg, wherein the dose is per capsule or per total number of minitabets in a capsule.

[1158] In some embodiments, the pharmaceutical agent comprises bacteria and/or mEVs and the dose of the pharmaceutical agent (e.g., bacteria and/or mEVs) is about 30 mg to about 1300 mg (by weight of bacteria and/or mEVs) (about 25, about 30, about 35, about 50, about 75, about 100, about 120, about 150, about 250, about 300, about 350, about 400, about 500, about 600, about 700, about 750, about 800, about 900, about 1000, about 1100, about 1200, about 1250, about 1300, about 2000, about 2500, about 3000, or about 3500 mg, wherein the dose is per capsule or per total number of minitabets in a capsule.

[1159] In some embodiments, the pharmaceutical agent comprises bacteria and/or mEVs and the dose of pharmaceutical agent (e.g., bacteria and/or mEVs) is about 2×10^6 to about 2×10^{16} particles (e.g., wherein particle count is determined by NTA (nanoparticle tracking analysis)), wherein the dose is per capsule or per total number of minitabets in a capsule.

[1160] In some embodiments, the pharmaceutical agent comprises bacteria and/or mEVs and the dose of pharmaceutical agent (e.g., bacteria and/or mEVs) is about 5 mg to about 900 mg total protein (e.g., wherein total protein is determined by Bradford assay or BCA), wherein the dose is per capsule or per total number of minitabets in a capsule.

[1161] In some embodiments, the solid dosage form further comprises one or more additional pharmaceutical agents.

[1162] In some embodiments, the solid dosage form further comprises an excipient (e.g., an excipient described herein, e.g., a diluent, a binder and/or an adhesive, a disintegrant, a lubricant and/or a glidant, a coloring agent, a flavoring agent, and/or a sweetening agent).

[1163] In some aspects, the disclosure provides a method for preparing a capsule comprising an enterically coated minitabset comprising a pharmaceutical agent (e.g., a therapeutically effective amount thereof), wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), the method comprising:

[1164] a) combining the pharmaceutical agent with a pharmaceutically acceptable excipient;

[1165] b) compressing the pharmaceutical agent and pharmaceutically acceptable excipient, thereby forming a minitabset;

[1166] c) enterically coating the minitabket (e.g., thereby preparing the enterically coated minitabket), and

[1167] d) loading the capsule with the enterically coated minitabket (e.g., a size 0 capsule can contain about 31 to about 35 (e.g., 33) minitabkets, wherein the minitabkets are 3mm in size),

[1168] thereby preparing the capsule.

[1169] In some embodiments, the method further comprises banding the capsule after loading the capsule. In some embodiments, the capsule is banded with an HPMC-based banding solution.

[1170] In some embodiments, the minitabket (e.g., enterically coated minitabket) is a 1mm minitabket, 1.5 mm minitabket, 2mm minitabket, 3mm minitabket, or 4mm minitabket. In some embodiments, the capsule is a size 00, size 0, size 1, size 2, size 3, size 4, or size 5 capsule. In some embodiments, the capsule comprises HPMC (hydroxyl propyl methyl cellulose) or gelatin.

[1171] In some embodiments, the enteric coating comprises one enteric coating.

[1172] In some embodiments, the enteric coating comprises an inner enteric coating and an outer enteric coating, and wherein the inner and outer enteric coatings are not identical (e.g., the inner and outer enteric coatings do not contain identical components in identical amounts).

[1173] In some embodiments, the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) comprises a polymethacrylate-based copolymer.

[1174] In some embodiments, the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) comprises a methacrylic acid ethyl acrylate (MAE) copolymer (1:1).

[1175] In some embodiments, the one enteric coating comprises methacrylic acid ethyl acrylate (MAE) copolymer (1:1) (such as Kollicoat MAE 100P).

[1176] In some embodiments, the one enteric coating comprises a Eudragit copolymer, e.g., a Eudragit L (e.g., Eudragit L 100-55; Eudragit L 30 D-55), a Eudragit S, a Eudragit RL, a Eudragit RS, a Eudragit E, or a Eudragit FS (e.g., Eudragit FS 30 D).

[1177] In some embodiments, the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) comprises cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), poly(vinyl acetate phthalate) (PVAP),

hydroxypropyl methylcellulose phthalate (HPMCP), a fatty acid, a wax, shellac (esters of aleuritic acid), a plastic, a plant fiber, zein, Aqua-Zein (an aqueous zein formulation containing no alcohol), amylose starch, a starch derivative, a dextrin, a methyl acrylate-methacrylic acid copolymer, cellulose acetate succinate, hydroxypropyl methyl cellulose acetate succinate (hypromellose acetate succinate), a methyl methacrylate-methacrylic acid copolymer, or sodium alginate.

[1178] In some embodiments, the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) comprises an anionic polymeric material.

[1179] In some embodiments, the pharmaceutical agent comprises bacteria.

[1180] In some embodiments, the pharmaceutical agent comprises microbial extracellular vesicles (mEV).

[1181] In some embodiments, the pharmaceutical agent comprises bacteria and microbial extracellular vesicles (mEV).

[1182] In some embodiments, the pharmaceutical agent has one or more beneficial immune effects outside the gastrointestinal tract, e.g., when the solid dosage form is orally administered.

[1183] In some embodiments, the pharmaceutical agent modulates immune effects outside the gastrointestinal tract (e.g., outside of the small intestine) in the subject, e.g., when the solid dosage form is orally administered.

[1184] In some embodiments, the pharmaceutical agent causes a systemic effect (e.g., an effect outside of the gastrointestinal tract), e.g., when the solid dosage form is orally administered.

[1185] In some embodiments, the pharmaceutical agent acts on immune cells and/or epithelial cells in the small intestine (e.g., causing a systemic effect (e.g., an effect outside of the gastrointestinal tract), e.g., when the solid dosage form is orally administered.

[1186] In some embodiments, the pharmaceutical agent comprises isolated bacteria (e.g., from one or more strains of bacteria (e.g., bacteria of interest) (e.g., a therapeutically effective amount thereof)). E.g., wherein at least 50%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% of the content of the pharmaceutical agent is the isolated bacteria (e.g., bacteria of interest).

- [1187] In some embodiments, the pharmaceutical agent comprises bacteria that have been gamma irradiated, UV irradiated, heat inactivated, acid treated, or oxygen sparged.
- [1188] In some embodiments, the pharmaceutical agent comprises live bacteria.
- [1189] In some embodiments, the pharmaceutical agent comprises dead bacteria.
- [1190] In some embodiments, the pharmaceutical agent comprises non-replicating bacteria.
- [1191] In some embodiments, the pharmaceutical agent comprises bacteria from one strain of microbe (e.g., bacteria).
- [1192] In some embodiments, the bacteria are lyophilized (e.g., the lyophilized product further comprises a pharmaceutically acceptable excipient) (e.g., a powder form).
- [1193] In some embodiments, the bacteria are gamma irradiated.
- [1194] In some embodiments, the bacteria are UV irradiated.
- [1195] In some embodiments, the bacteria are heat inactivated (e.g., at 50°C for two hours or at 90°C for two hours).
- [1196] In some embodiments, the bacteria are acid treated.
- [1197] In some embodiments, the bacteria are oxygen sparged (e.g., at 0.1 vvm for two hours).
- [1198] In some embodiments, the bacteria are Gram positive bacteria.
- [1199] In some embodiments, the bacteria are Gram negative bacteria.
- [1200] In some embodiments, the bacteria are aerobic bacteria.
- [1201] In some embodiments, the bacteria are anaerobic bacteria. In some embodiments, the anaerobic bacteria comprise obligate anaerobes. In some embodiments, the anaerobic bacteria comprise facultative anaerobes.
- [1202] In some embodiments, the bacteria are acidophile bacteria.
- [1203] In some embodiments, the bacteria are alkaliphile bacteria.
- [1204] In some embodiments, the bacteria are neutrophile bacteria.
- [1205] In some embodiments, the bacteria are fastidious bacteria.
- [1206] In some embodiments, the bacteria are nonfastidious bacteria.
- [1207] In some embodiments, the bacteria are of a taxonomic group (e.g., class, order, family, genus, species or strain) listed in Table 1, Table 2, or Table 3.
- [1208] In some embodiments, the bacteria are a bacterial strain listed in Table 1, Table 2, or Table 3.

[1209] In some embodiments, the bacteria are of a taxonomic group (e.g., class, order, family, genus, species or strain) listed in Table J.

[1210] In some embodiments, the bacteria are a bacterial strain listed in Table J.

[1211] In some embodiments, the Gram negative bacteria belong to class *Negativicutes*.

[1212] In some embodiments, the Gram negative bacteria belong to family *Veillonellaceae*, *Selenomonadaceae*, *Acidaminococcaceae*, or *Sporomusaceae*.

[1213] In some embodiments, the bacteria of the genus *Megasphaera*, *Selenomonas*, *Propionospora*, or *Acidaminococcus*.

[1214] In some embodiments, the bacteria are *Megasphaera* sp., *Selenomonas felix*, *Acidaminococcus intestine*, or *Propionospora* sp. bacteria.

[1215] In some embodiments, the bacteria are of the genus *Lactococcus*, *Prevotella*, *Bifidobacterium*, or *Veillonella*.

[1216] In some embodiments, the bacteria are *Lactococcus lactis cremoris* bacteria.

[1217] In some embodiments, the bacteria are *Prevotella histicola* bacteria.

[1218] In some embodiments, the bacteria are *Bifidobacterium animalis* bacteria.

[1219] In some embodiments, the bacteria are *Veillonella parvula* bacteria.

[1220] In some embodiments, the bacteria are *Lactococcus lactis cremoris* bacteria.

In some embodiments, the *Lactococcus lactis cremoris* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the *Lactococcus* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the *Lactococcus* bacteria are *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368).

[1221] In some embodiments, the bacteria are *Prevotella* bacteria. In some embodiments, the *Prevotella* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Prevotella* Strain B 50329 (NRRL accession number B 50329). In some embodiments, the *Prevotella* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Prevotella* Strain B 50329 (NRRL

accession number B 50329). In some embodiments, the *Prevotella* bacteria are *Prevotella* Strain B 50329 (NRRL accession number B 50329).

[1222] In some embodiments, the bacteria are *Bifidobacterium* bacteria. In some embodiments, the *Bifidobacterium* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097. In some embodiments, the *Bifidobacterium* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097. In some embodiments, the *Bifidobacterium* bacteria are *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097.

[1223] In some embodiments, the bacteria are *Veillonella* bacteria. In some embodiments, the *Veillonella* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the *Veillonella* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the *Veillonella* bacteria are *Veillonella* bacteria deposited as ATCC designation number PTA-125691.

[1224] In some embodiments, the bacteria are from *Ruminococcus gnavus* bacteria. In some embodiments, the *Ruminococcus gnavus* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695.

[1225] In some embodiments, the bacteria are *Megasphaera sp.* bacteria. In some embodiments, the *Megasphaera sp.* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some

embodiments, the *Megasphaera sp.* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some embodiments, the *Megasphaera sp.* bacteria are *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770.

[1226] In some embodiments, the bacteria are *Fournierella massiliensis* bacteria. In some embodiments, the *Fournierella massiliensis* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696.

[1227] In some embodiments, the bacteria are *Harryflintia acetispora* bacteria. In some embodiments, the *Harryflintia acetispora* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694.

[1228] In some embodiments, the bacteria are of the family *Acidaminococcaceae*, *Alcaligenaceae*, *Akkermansiaceae*, *Bacteriodaceae*, *Bifidobacteriaceae*, *Burkholderiaceae*, *Catabacteriaceae*, *Clostridiaceae*, *Coriobacteriaceae*, *Enterobacteriaceae*, *Enterococcaceae*, *Fusobacteriaceae*, *Lachnospiraceae*, *Listeraceae*, *Mycobacteriaceae*, *Neisseriaceae*, *Odoribacteraceae*, *Oscillospiraceae*, *Peptococcaceae*, *Peptostreptococcaceae*, *Porphyromonadaceae*, *Prevotellaceae*, *Propionibacteraceae*, *Rikenellaceae*, *Ruminococcaceae*, *Selenomonadaceae*, *Sporomusaceae*, *Streptococcaceae*, *Streptomycetaceae*, *Sutterellaceae*, *Synergistaceae*, or *Veillonellaceae*.

[1229] In some embodiments, the bacteria are of the genus *Akkermansia*, *Christensenella*, *Blautia*, *Enterococcus*, *Eubacterium*, *Roseburia*, *Bacteroides*, *Parabacteroides*, or *Erysipelatoclostridium*.

[1230] In some embodiments, the bacteria are *Blautia hydrogenotrophica*, *Blautia stercoris*, *Blautia wexlerae*, *Eubacterium faecium*, *Eubacterium contortum*, *Eubacterium rectale*, *Enterococcus faecalis*, *Enterococcus durans*, *Enterococcus villorum*, *Enterococcus gallinarum*; *Bifidobacterium lactis*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, *Bifidobacterium animalis*, or *Bifidobacterium breve* bacteria.

[1231] In some embodiments, the bacteria are BCG (*Bacillus Calmette-Guerin*), *Parabacteroides*, *Blautia*, *Veillonella*, *Lactobacillus salivarius*, *Agathobaculum*, *Ruminococcus gnavus*, *Paraclostridium benzoelyticum*, *Turicibacter sanguinus*, *Burkholderia*, *Klebsiella quasipneumoniae ssp similpneumoniae*, *Klebsiella oxytoca*, *Tyzzera nexilis*, or *Neisseria* bacteria.

[1232] In some embodiments, the bacteria are *Blautia hydrogenotrophica* bacteria.

[1233] In some embodiments, the bacteria are *Blautia stercoris* bacteria.

[1234] In some embodiments, the bacteria are *Blautia wexlerae* bacteria.

[1235] In some embodiments, the bacteria are *Enterococcus gallinarum* bacteria.

[1236] In some embodiments, the bacteria are *Enterococcus faecium* bacteria.

[1237] In some embodiments, the bacteria are *Bifidobacterium bifidum* bacteria.

[1238] In some embodiments, the bacteria are *Bifidobacterium breve* bacteria.

[1239] In some embodiments, the bacteria are *Bifidobacterium longum* bacteria.

[1240] In some embodiments, the bacteria are *Roseburia hominis* bacteria.

[1241] In some embodiments, the bacteria are *Bacteroides thetaiotaomicron* bacteria.

[1242] In some embodiments, the bacteria are *Bacteroides coprocola* bacteria.

[1243] In some embodiments, the bacteria are *Erysipelatoclostridium ramosum* bacteria.

[1244] In some embodiments, the bacteria are *Megasphaera massiliensis* bacteria.

[1245] In some embodiments, the bacteria are *Eubacterium* bacteria.

[1246] In some embodiments, the bacteria are *Parabacteroides distasonis* bacteria.

[1247] In some embodiments, the bacteria are *Lactobacillus plantarum* bacteria.

[1248] In some embodiments, the bacteria are bacteria of the *Negativicutes* class.

[1249] In some embodiments, the bacteria are of the *Veillonellaceae* family.

- [1250] In some embodiments, the bacteria are of the *Selenomonadaceae* family.
- [1251] In some embodiments, the bacteria are of the *Acidaminococcaceae* family.
- [1252] In some embodiments, the bacteria are of the *Sporomusaceae* family.
- [1253] In some embodiments, the bacteria are of the *Megasphaera* genus.
- [1254] In some embodiments, the bacteria are of the *Selenomonas* genus.
- [1255] In some embodiments, the bacteria are of the *Propionospora* genus.
- [1256] In some embodiments, the bacteria are of the *Acidaminococcus* genus.
- [1257] In some embodiments, the bacteria are *Megasphaera sp.* bacteria.
- [1258] In some embodiments, the bacteria are *Selenomonas felix* bacteria.
- [1259] In some embodiments, the bacteria are *Acidaminococcus intestini* bacteria.
- [1260] In some embodiments, the bacteria are *Propionospora sp.* bacteria.
- [1261] In some embodiments, the bacteria are bacteria of the *Clostridia* class.
- [1262] In some embodiments, the bacteria are of the *Oscillospiraceae* family.
- [1263] In some embodiments, the bacteria are of the *Faecalibacterium* genus.
- [1264] In some embodiments, the bacteria are of the *Fournierella* genus.
- [1265] In some embodiments, the bacteria are of the *Harryflintia* genus.
- [1266] In some embodiments, the bacteria are of the *Agathobaculum* genus.
- [1267] In some embodiments, the bacteria are *Faecalibacterium prausnitzii* (e.g., *Faecalibacterium prausnitzii* Strain A) bacteria.
- [1268] In some embodiments, the bacteria are *Fournierella massiliensis* (e.g., *Fournierella massiliensis* Strain A) bacteria.
- [1269] In some embodiments, the bacteria are *Harryflintia acetispora* (e.g., *Harryflintia acetispora* Strain A) bacteria.
- [1270] In some embodiments, the bacteria are *Agathobaculum sp.* (e.g., *Agathobaculum sp.* Strain A) bacteria.
- [1271] In some embodiments, the bacteria are a strain of *Agathobaculum sp.* In some embodiments, the *Agathobaculum sp.* strain is a strain comprising at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity (e.g., at least 99.5% sequence identity, at least 99.6% sequence identity, at least 99.7% sequence identity, at least 99.8% sequence identity, at least 99.9% sequence identity) to the nucleotide sequence (e.g., genomic sequence, 16S sequence, CRISPR sequence) of the *Agathobaculum sp.* Strain A (ATCC Deposit Number PTA-125892). In some embodiments, the

Agathobaculum sp. strain is the *Agathobaculum* sp. Strain A (ATCC Deposit Number PTA-125892).

[1272] In some embodiments, the bacteria are of the class *Bacteroidia* [phylum *Bacteroidota*]. In some embodiments, the bacteria are of order *Bacteroidales*. In some embodiments, the bacteria are of the family *Porphyromonadaceae*. In some embodiments, the bacteria are of the family *Prevotellaceae*. In some embodiments, the bacteria are of the class *Bacteroidia* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the bacteria are of the class *Bacteroidia* that stain Gram negative. In some embodiments, the bacteria are of the class *Bacteroidia* wherein the bacteria is diderm and the bacteria stain Gram negative.

[1273] In some embodiments, the bacteria are of the class *Clostridia* [phylum *Firmicutes*]. In some embodiments, the bacteria are of the order *Eubacteriales*. In some embodiments, the bacteria are of the family *Oscillispiraceae*. In some embodiments, the bacteria are of the family *Lachnospiraceae*. In some embodiments, the bacteria are of the family *Peptostreptococcaceae*. In some embodiments, the bacteria are of the family *Clostridiales* family XIII/ *Incertae sedis* 41. In some embodiments, the bacteria are of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm. In some embodiments, the bacteria are of the class *Clostridia* that stain Gram negative. In some embodiments, the bacteria are of the class *Clostridia* that stain Gram positive. In some embodiments, the bacteria are of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram negative. In some embodiments, the bacteria are of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram positive.

[1274] In some embodiments, the bacteria are of the class *Negativicutes* [phylum *Firmicutes*]. In some embodiments, the bacteria are of the order *Veillonellales*. In some embodiments, the bacteria are of the family *Veillonelloceae*. In some embodiments, the bacteria are of the order *Selenomonadales*. In some embodiments, the bacteria are of the family *Selenomonadaceae*. In some embodiments, the bacteria are of the family *Sporomusaceae*. In some embodiments, the bacteria are of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the bacteria are of the class *Negativicutes* that stain Gram negative. In some embodiments, the bacteria are of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[1275] In some embodiments, the bacteria are of the class *Synergistia* [phylum *Synergistota*]. In some embodiments, the bacteria are of the order *Synergistales*. In some embodiments, the bacteria are of the family *Synergistaceae*. In some embodiments, the bacteria are of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the bacteria are of the class *Synergistia* that stain Gram negative. In some embodiments, the bacteria are of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[1276] In some embodiments, the bacteria are bacteria that produce metabolites, e.g., the bacteria produce butyrate, iosine, propionate, or tryptophan metabolites.

[1277] In some embodiments, the bacteria produce butyrate. In some embodiments, the bacteria are from the genus *Blautia*; *Christensella*; *Copracoccus*; *Eubacterium*; *Lachnospiraceae*; *Megasphaera*; or *Roseburia*.

[1278] In some embodiments, the bacteria produce iosine. In some embodiments, the bacteria are from the genus *Bifidobacterium*; *Lactobacillus*; or *Olsenella*.

[1279] In some embodiments, the bacteria produce propionate. In some embodiments, the bacteria are from the genus *Akkermansia*; *Bacteriodes*; *Dialister*; *Eubacterium*; *Megasphaera*; *Parabacteriodes*; *Prevotella*; *Ruminococcus*; or *Veillonella*.

[1280] In some embodiments, the bacteria produce tryptophan metabolites. In some embodiments, the bacteria are from the genus *Lactobacillus* or *Peptostreptococcus*.

[1281] In some embodiments, the bacteria are bacteria that produce inhibitors of histone deacetylase 3 (HDAC3). In some embodiments, the bacteria are from the species *Bariatricus massiliensis*, *Faecalibacterium prausnitzii*, *Megasphaera massiliensis* or *Roseburia intestinalis*.

[1282]

[1283] In some embodiments, the pharmaceutical agent comprises isolated mEVs (e.g., from one or more strains of bacteria (e.g., bacteria of interest)) (e.g., a therapeutically effective amount thereof). E.g., wherein at least 50%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% of the content of the pharmaceutical agent is isolated mEV of bacteria (e.g., bacteria of interest).

[1284] In some embodiments, the pharmaceutical agent comprises mEVs and the mEVs comprise secreted mEVs (smEVs).

[1285] In some embodiments, the pharmaceutical agent comprises mEVs and the mEVs comprise processed mEVs (pmEVs).

[1286] In some embodiments, the pharmaceutical agent comprises pmEVs and the pmEVs are produced from bacteria that have been gamma irradiated, UV irradiated, heat inactivated, acid treated, or oxygen sparged.

[1287] In some embodiments, the pharmaceutical agent comprises pmEVs and the pmEVs are produced from live bacteria.

[1288] In some embodiments, the pharmaceutical agent comprises pmEVs and the pmEVs are produced from dead bacteria.

[1289] In some embodiments, the pharmaceutical agent comprises pmEVs and the pmEVs are produced from non-replicating bacteria.

[1290] In some embodiments, the pharmaceutical agent comprises mEVs and the mEVs are from one strain of bacteria.

[1291] In some embodiments, the mEVs are lyophilized (e.g., the lyophilized product further comprises a pharmaceutically acceptable excipient).

[1292] In some embodiments, the mEVs are gamma irradiated.

[1293] In some embodiments, the mEVs are UV irradiated.

[1294] In some embodiments, the mEVs are heat inactivated (e.g., at 50°C for two hours or at 90°C for two hours).

[1295] In some embodiments, the mEVs are acid treated.

[1296] In some embodiments, the mEVs are oxygen sparged (e.g., at 0.1 vvm for two hours).

[1297] In some embodiments, the mEVs are from Gram positive bacteria.

[1298] In some embodiments, the mEVs are from Gram negative bacteria.

[1299] In some embodiments, the mEVs are from aerobic bacteria.

[1300] In some embodiments, the mEVs are from anaerobic bacteria. In some embodiments, the anaerobic bacteria comprise obligate anaerobes. In some embodiments, the anaerobic bacteria comprise facultative anaerobes.

[1301] In some embodiments, the mEVs are from acidophile bacteria.

[1302] In some embodiments, the mEVs are from alkaliphile bacteria.

[1303] In some embodiments, the mEVs are from neutrophile bacteria.

[1304] In some embodiments, the mEVs are from fastidious bacteria.

[1305] In some embodiments, the mEVs are from nonfastidious bacteria.

[1306] In some embodiments, the mEVs are from bacteria of a taxonomic group (e.g., class, order, family, genus, species or strain) listed in Table 1, Table 2, or Table 3.

- [1307] In some embodiments, the mEVs are from a bacterial strain listed in Table 1, Table 2, or Table 3.
- [1308] In some embodiments, the mEVs are from bacteria of a taxonomic group (e.g., class, order, family, genus, species or strain) listed in Table J.
- [1309] In some embodiments, the mEVs are from a bacterial strain listed in Table J.
- [1310] In some embodiments, the Gram negative bacteria belong to class *Negativicutes*.
- [1311] In some embodiments, the Gram negative bacteria belong to family *Veillonellaceae*, *Selenomonadaceae*, *Acidaminococcaceae*, or *Sporomusaceae*.
- [1312] In some embodiments, the mEVs are from bacteria of the genus *Megasphaera*, *Selenomonas*, *Propionospora*, or *Acidaminococcus*.
- [1313] In some embodiments, the mEVs are *Megasphaera sp.*, *Selenomonas felix*, *Acidaminococcus intestine*, or *Propionospora sp.* bacteria.
- [1314] In some embodiments, the mEVs are from bacteria of the genus *Lactococcus*, *Prevotella*, *Bifidobacterium*, or *Veillonella*.
- [1315] In some embodiments, the mEVs are from *Lactococcus lactis cremoris* bacteria.
- [1316] In some embodiments, the mEVs are from *Prevotella histicola* bacteria.
- [1317] In some embodiments, the mEVs are from *Bifidobacterium animalis* bacteria.
- [1318] In some embodiments, the mEVs are from *Veillonella parvula* bacteria.
- [1319] In some embodiments, the mEVs are from *Lactococcus lactis cremoris* bacteria. In some embodiments, the *Lactococcus lactis cremoris* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the *Lactococcus* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the *Lactococcus* bacteria are from *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368).
- [1320] In some embodiments, the mEVs are from *Prevotella* bacteria. In some embodiments, the *Prevotella* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the

Prevotella Strain B 50329 (NRRL accession number B 50329). In some embodiments, the *Prevotella* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Prevotella* Strain B 50329 (NRRL accession number B 50329). In some embodiments, the *Prevotella* bacteria are from *Prevotella* Strain B 50329 (NRRL accession number B 50329).

[1321] In some embodiments, the mEVs are from *Bifidobacterium* bacteria. In some embodiments, the *Bifidobacterium* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097. In some embodiments, the *Bifidobacterium* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097. In some embodiments, the *Bifidobacterium* bacteria are from *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097.

[1322] In some embodiments, the mEVs are from *Veillonella* bacteria. In some embodiments, the *Veillonella* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the *Veillonella* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the *Veillonella* bacteria are from *Veillonella* bacteria deposited as ATCC designation number PTA-125691.

[1323] In some embodiments, the mEVs are from *Ruminococcus gnavus* bacteria. In some embodiments, the *Ruminococcus gnavus* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are from *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695.

[1324] In some embodiments, the mEVs are from *Megasphaera sp.* bacteria. In some embodiments, the *Megasphaera sp.* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some embodiments, the *Megasphaera sp.* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some embodiments, the *Megasphaera sp.* bacteria are from *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770.

[1325] In some embodiments, the mEVs are from *Fournierella massiliensis* bacteria. In some embodiments, the *Fournierella massiliensis* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are from *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696.

[1326] In some embodiments, the mEVs are from *Harryflintia acetispora* bacteria. In some embodiments, the *Harryflintia acetispora* bacteria are from a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are from a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are from *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694.

[1327] In some embodiments, the mEVs are from bacteria of the family *Acidaminococcaceae*, *Alcaligenaceae*, *Akkermansiaceae*, *Bacteriodaceae*, *Bifidobacteriaceae*, *Burkholderiaceae*, *Catabacteriaceae*, *Clostridiaceae*, *Coriobacteriaceae*, *Enterobacteriaceae*, *Enterococcaceae*, *Fusobacteriaceae*, *Lachnospiraceae*, *Listeraceae*, *Mycobacteriaceae*, *Neisseriaceae*, *Odoribacteraceae*,

Oscillospiraceae, Peptococcaceae, Peptostreptococcaceae, Porphyromonadaceae, Prevotellaceae, Propionibacteraceae, Rikenellaceae, Ruminococcaceae, Selenomonadaceae, Sporomusaceae, Streptococcaceae, Streptomyetaceae, Sutterellaceae, Synergistaceae, or Veillonellaceae.

[1328] In some embodiments, the mEVs are from bacteria of the genus *Akkermansia, Christensenella, Blautia, Enterococcus, Eubacterium, Roseburia, Bacteroides, Parabacteroides, or Erysipelatoclostridium.*

[1329] In some embodiments, the mEVs are from *Blautia hydrogenotrophica, Blautia stercoris, Blautia wexlerae, Eubacterium faecium, Eubacterium contortum, Eubacterium rectale, Enterococcus faecalis, Enterococcus durans, Enterococcus villorum, Enterococcus gallinarum; Bifidobacterium lactis, Bifidobacterium bifidum, Bifidobacterium longum, Bifidobacterium animalis, or Bifidobacterium breve* bacteria.

[1330] In some embodiments, the mEVs are from *BCG (bacillus Calmette-Guerin), Parabacteroides, Blautia, Veillonella, Lactobacillus salivarius, Agathobaculum, Ruminococcus gnavus, Paraclostridium benzoelyticum, Turicibacter sanguinus, Burkholderia, Klebsiella quasipneumoniae ssp similpneumoniae, Klebsiella oxytoca, Tyzzerella nexilis, or Neisseria* bacteria.

[1331] In some embodiments, the mEVs are from *Blautia hydrogenotrophica* bacteria.

[1332] In some embodiments, the mEVs are from *Blautia stercoris* bacteria.

[1333] In some embodiments, the mEVs are from *Blautia wexlerae* bacteria.

[1334] In some embodiments, the mEVs are from *Enterococcus gallinarum* bacteria.

[1335] In some embodiments, the mEVs are from *Enterococcus faecium* bacteria.

[1336] In some embodiments, the mEVs are from *Bifidobacterium bifidum* bacteria.

[1337] In some embodiments, the mEVs are from *Bifidobacterium breve* bacteria.

[1338] In some embodiments, the mEVs are from *Bifidobacterium longum* bacteria.

[1339] In some embodiments, the mEVs are from *Roseburia hominis* bacteria.

[1340] In some embodiments, the mEVs are from *Bacteroides thetaiotaomicron* bacteria.

[1341] In some embodiments, the mEVs are from *Bacteroides coprocola* bacteria.

- [1342] In some embodiments, the mEVs are from *Erysipelatoclostridium ramosum* bacteria.
- [1343] In some embodiments, the mEVs are from *Megasphaera massiliensis* bacteria.
- [1344] In some embodiments, the mEVs are from *Eubacterium* bacteria.
- [1345] In some embodiments, the mEVs are from *Parabacteroides distasonis* bacteria.
- [1346] In some embodiments, the mEVs are from *Lactobacillus plantarum* bacteria.
- [1347] In some embodiments, the mEVs are from bacteria of the *Negativicutes* class.
- [1348] In some embodiments, the mEVs are from bacteria of the *Veillonellaceae* family.
- [1349] In some embodiments, the mEVs are from bacteria of the *Selenomonadaceae* family.
- [1350] In some embodiments, the mEVs are from bacteria of the *Acidaminococcaceae* family.
- [1351] In some embodiments, the mEVs are from bacteria of the *Sporomusaceae* family.
- [1352] In some embodiments, the mEVs are from bacteria of the *Megasphaera* genus.
- [1353] In some embodiments, the mEVs are from bacteria of the *Selenomonas* genus.
- [1354] In some embodiments, the mEVs are from bacteria of the *Propionospora* genus.
- [1355] In some embodiments, the mEVs are from bacteria of the *Acidaminococcus* genus.
- [1356] In some embodiments, the mEVs are from *Megasphaera sp.* bacteria.
- [1357] In some embodiments, the mEVs are from *Selenomonas felix* bacteria.
- [1358] In some embodiments, the mEVs are from *Acidaminococcus intestini* bacteria.
- [1359] In some embodiments, the mEVs are from *Propionospora sp.* bacteria.
- [1360] In some embodiments, the mEVs are from bacteria of the *Clostridia* class.

- [1361] In some embodiments, the mEVs are from bacteria of the *Oscillospiraceae* family.
- [1362] In some embodiments, the mEVs are from bacteria of the *Faecalibacterium* genus.
- [1363] In some embodiments, the mEVs are from bacteria of the *Fournierella* genus.
- [1364] In some embodiments, the mEVs are from bacteria of the *Harryflintia* genus.
- [1365] In some embodiments, the mEVs are from bacteria of the *Agathobaculum* genus.
- [1366] In some embodiments, the mEVs are from *Faecalibacterium prausnitzii* (e.g., *Faecalibacterium prausnitzii* Strain A) bacteria.
- [1367] In some embodiments, the mEVs are from *Fournierella massiliensis* (e.g., *Fournierella massiliensis* Strain A) bacteria.
- [1368] In some embodiments, the mEVs are from *Harryflintia acetispora* (e.g., *Harryflintia acetispora* Strain A) bacteria.
- [1369] In some embodiments, the mEVs are from *Agathobaculum sp.* (e.g., *Agathobaculum sp.* Strain A) bacteria.
- [1370] In some embodiments, the mEVs are from a strain of *Agathobaculum sp.* In some embodiments, the *Agathobaculum sp.* strain is a strain comprising at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity (e.g., at least 99.5% sequence identity, at least 99.6% sequence identity, at least 99.7% sequence identity, at least 99.8% sequence identity, at least 99.9% sequence identity) to the nucleotide sequence (e.g., genomic sequence, 16S sequence, CRISPR sequence) of the *Agathobaculum sp.* Strain A (ATCC Deposit Number PTA-125892). In some embodiments, the *Agathobaculum sp.* strain is the *Agathobaculum sp.* Strain A (ATCC Deposit Number PTA-125892).
- [1371] In some embodiments, the mEVs are from bacteria of the class *Bacteroidia* [phylum *Bacteroidota*]. In some embodiments, the mEVs are from bacteria of order *Bacteroidales*. In some embodiments, the mEVs are from bacteria of the family *Porphyromonadaceae*. In some embodiments, the mEVs are from bacteria of the family *Prevotellaceae*. In some embodiments, the mEVs are from bacteria of the class *Bacteroidia* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the mEVs are from bacteria of the class *Bacteroidia* that stain Gram negative. In some

embodiments, the mEVs are from bacteria of the class *Bacteroidia* wherein the bacteria is diderm and the bacteria stain Gram negative.

[1372] In some embodiments, the mEVs are from bacteria of the class *Clostridia* [phylum *Firmicutes*]. In some embodiments, the mEVs are from bacteria of the order *Eubacteriales*. In some embodiments, the mEVs are from bacteria of the family *Oscillispiraceae*. In some embodiments, the mEVs are from bacteria of the family *Lachnospiraceae*. In some embodiments, the mEVs are from bacteria of the family *Peptostreptococcaceae*. In some embodiments, the mEVs are from bacteria of the family *Clostridiales* family XIII/*Incertae sedis* 41. In some embodiments, the mEVs are from bacteria of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm. In some embodiments, the mEVs are from bacteria of the class *Clostridia* that stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Clostridia* that stain Gram positive. In some embodiments, the mEVs are from bacteria of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram positive.

[1373] In some embodiments, the mEVs are from bacteria of the class *Negativicutes* [phylum *Firmicutes*]. In some embodiments, the mEVs are from bacteria of the order *Veillonellales*. In some embodiments, the mEVs are from bacteria of the family *Veillonelloceae*. In some embodiments, the mEVs are from bacteria of the order *Selenomonadales*. In some embodiments, the mEVs are from bacteria of the family *Selenomonadaceae*. In some embodiments, the mEVs are from bacteria of the family *Sporomusaceae*. In some embodiments, the mEVs are from bacteria of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the mEVs are from bacteria of the class *Negativicutes* that stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[1374] In some embodiments, the mEVs are from bacteria of the class *Synergistia* [phylum *Synergistota*]. In some embodiments, the mEVs are from bacteria of the order *Synergistales*. In some embodiments, the mEVs are from bacteria of the family *Synergistaceae*. In some embodiments, the mEVs are from bacteria of the class *Synergistia*

wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the mEVs are from bacteria of the class *Synergistia* that stain Gram negative. In some embodiments, the mEVs are from bacteria of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[1375] In some embodiments, the mEVs are from bacteria that produce metabolites, e.g., the bacteria produce butyrate, iosine, propionate, or tryptophan metabolites.

[1376] In some embodiments, the bacteria produce butyrate. In some embodiments, the bacteria are from the genus *Blautia*; *Christensella*; *Copracoccus*; *Eubacterium*; *Lachnospiraceae*; *Megasphaera*; or *Roseburia*.

[1377] In some embodiments, the bacteria produce iosine. In some embodiments, the bacteria are from the genus *Bifidobacterium*; *Lactobacillus*; or *Olsenella*.

[1378] In some embodiments, the bacteria produce propionate. In some embodiments, the bacteria are from the genus *Akkermansia*; *Bacteriodes*; *Dialister*; *Eubacterium*; *Megasphaera*; *Parabacteriodes*; *Prevotella*; *Ruminococcus*; or *Veillonella*.

[1379] In some embodiments, the bacteria produce tryptophan metabolites. In some embodiments, the bacteria are from the genus *Lactobacillus* or *Peptostreptococcus*.

[1380] In some embodiments, the mEVs are from bacteria that produce inhibitors of histone deacetylase 3 (HDAC3). In some embodiments, the bacteria are from the species *Bariatricus massiliensis*, *Faecalibacterium prausnitzii*, *Megasphaera massiliensis* or *Roseburia intestinalis*.

[1381] In some embodiments, the pharmaceutical agent comprises bacteria and the dose of bacteria is about 1×10^7 to about 2×10^{12} (e.g., about 3×10^{10} or about 1.5×10^{11} or about 1.5×10^{12}) cells (e.g., wherein cell number is determined by total cell count, which is determined by Coulter counter), wherein the dose is per capsule or per total number of minitabets in a capsule. In some embodiments, the pharmaceutical agent comprises bacteria and the dose of bacteria is about 1×10^{10} to about 2×10^{12} (e.g., about 1.6×10^{11} or about 8×10^{11} or about 9.6×10^{11} or about 12.8×10^{11} or about 1.6×10^{12}) cells (e.g., wherein cell number is determined by total cell count, which is determined by Coulter counter), wherein the dose is per capsule or per total number of minitabets in a capsule.

[1382] In some embodiments, the pharmaceutical agent comprises bacteria and the dose of bacteria is about 1×10^9 , about 3×10^9 , about 5×10^9 , about 1.5×10^{10} , about 3×10^{10} , about 5×10^{10} , about 1.5×10^{11} , about 1.5×10^{12} , or about 2×10^{12} cells, wherein the dose is per capsule or per total number of minitabets in a capsule.

[1383] In some embodiments, the pharmaceutical agent comprises mEVs and the dose of mEVs is about 1×10^5 to about 7×10^{13} particles (e.g., wherein particle count is determined by NTA (nanoparticle tracking analysis)), wherein the dose is per capsule or per total number of minitabets in a capsule. In some embodiments, the pharmaceutical agent comprises mEVs and the dose of mEVs is about 1×10^{10} to about 7×10^{13} particles (e.g., wherein particle count is determined by NTA (nanoparticle tracking analysis)), wherein the dose is per capsule or per total number of minitabets in a capsule.

[1384] In some embodiments, the pharmaceutical agent comprises bacteria and/or mEVs and the dose of pharmaceutical agent (e.g., bacteria and/or mEVs) is about 10 mg to about 3500 mg, wherein the dose is per capsule or per total number of minitabets in a capsule.

[1385] In some embodiments, the pharmaceutical agent comprises bacteria and/or mEVs and the dose of drug substance that contains the pharmaceutical agent (e.g., bacteria and/or mEVs) is about 30 mg to about 1300 mg (by weight of bacteria and/or mEVs) (about 25, about 30, about 35, about 50, about 75, about 100, about 120, about 150, about 250, about 300, about 350, about 400, about 500, about 600, about 700, about 750, about 800, about 900, about 1000, about 1100, about 1200, about 1250, about 1300, about 2000, about 2500, about 3000, or about 3500 mg, wherein the dose is per capsule or per total number of minitabets in a capsule).

[1386] In some embodiments, the pharmaceutical agent comprises bacteria and/or mEVs and the dose of pharmaceutical agent (e.g., bacteria and/or mEVs) is about 2×10^6 to about 2×10^{16} particles (e.g., wherein particle count is determined by NTA (nanoparticle tracking analysis)), wherein the dose is per capsule or per total number of minitabets in a capsule.

[1387] In some embodiments, the pharmaceutical agent comprises bacteria and/or mEVs and the dose of pharmaceutical agent (e.g., bacteria and/or mEVs) is about 5 mg to about 900 mg total protein (e.g., wherein total protein is determined by Bradford assay or BCA), wherein the dose is per capsule or per total number of minitabets in a capsule.

[1388] In some embodiments, the capsule or minitabets further comprises one or more additional pharmaceutical agents.

[1389] In some embodiments, the capsule or minitablet further comprises an excipient (e.g., an excipient described herein, e.g., a diluent, a binder and/or an adhesive, a disintegrant, a lubricant and/or a glidant, a coloring agent, a flavoring agent, and/or a sweetening agent).

Brief Description of the Drawings

[1390] **Figure 1** is a graph showing the effects of *L. Lactis* spp. *cremoris* solid dosage forms on ear thickness 24 hours after challenge in a DTH model.

Detailed Description

Definitions

[1391] “Adjuvant” or “Adjuvant therapy” broadly refers to an agent that affects an immunological or physiological response in a subject (e.g., human). For example, an adjuvant might increase the presence of an antigen over time or to an area of interest like a tumor, help absorb an antigen presenting cell antigen, activate macrophages and lymphocytes and support the production of cytokines. By changing an immune response, an adjuvant might permit a smaller dose of an immune interacting agent to increase the effectiveness or safety of a particular dose of the immune interacting agent. For example, an adjuvant might prevent T cell exhaustion and thus increase the effectiveness or safety of a particular immune interacting agent.

[1392] “Administration” broadly refers to a route of administration of a composition (e.g., a pharmaceutical composition such as a solid dosage form that contains a pharmaceutical agent as described herein) to a subject. Examples of routes of administration include oral administration, rectal administration, topical administration, inhalation (nasal) or injection. Administration by injection includes intravenous (IV), intramuscular (IM), intratumoral (IT) and subcutaneous (SC) administration. A pharmaceutical composition described herein can be administered in any form by any effective route, including but not limited to intratumoral, oral, parenteral, enteral, intravenous, intraperitoneal, topical, transdermal (e.g., using any standard patch), intradermal, ophthalmic, (intra)nasally, local, non-oral, such as aerosol, inhalation, subcutaneous, intramuscular, buccal, sublingual, (trans)rectal, vaginal, intra-arterial, and intrathecal, transmucosal (e.g., sublingual, lingual, (trans)buccal, (trans)urethral, vaginal (e.g., trans- and perivaginally), implanted, intravesical, intrapulmonary, intraduodenal,

intra-gastric, and intra-bronchial. In preferred embodiments, a pharmaceutical composition described herein is administered orally, rectally, intratumorally, topically, intravesically, by injection into or adjacent to a draining lymph node, intravenously, by inhalation or aerosol, or subcutaneously. In another preferred embodiment, a pharmaceutical composition described herein is administered orally, intratumorally, or intravenously. In another embodiment, a pharmaceutical composition described herein is administered orally.

[1393] As used herein, the term “antibody” may refer to both an intact antibody and an antigen binding fragment thereof. Intact antibodies are glycoproteins that include at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain includes a heavy chain variable region (abbreviated herein as V_H) and a heavy chain constant region. Each light chain includes a light chain variable region (abbreviated herein as V_L) and a light chain constant region. The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The term “antibody” includes, for example, monoclonal antibodies, polyclonal antibodies, chimeric antibodies, humanized antibodies, human antibodies, multispecific antibodies (*e.g.*, bispecific antibodies), single-chain antibodies and antigen-binding antibody fragments.

[1394] The terms “antigen binding fragment” and “antigen-binding portion” of an antibody, as used herein, refer to one or more fragments of an antibody that retain the ability to bind to an antigen. Examples of binding fragments encompassed within the term “antigen-binding fragment” of an antibody include Fab, Fab', F(ab')₂, Fv, scFv, disulfide linked Fv, Fd, diabodies, single-chain antibodies, NANOBOBIES®, isolated CDRH3, and other antibody fragments that retain at least a portion of the variable region of an intact antibody. These antibody fragments can be obtained using conventional recombinant and/or enzymatic techniques and can be screened for antigen binding in the same manner as intact antibodies.

[1395] “Cancer” broadly refers to an uncontrolled, abnormal growth of a host’s own cells leading to invasion of surrounding tissue and potentially tissue distal to the initial site of abnormal cell growth in the host. Major classes include carcinomas which are cancers of

the epithelial tissue (*e.g.*, skin, squamous cells); sarcomas which are cancers of the connective tissue (*e.g.*, bone, cartilage, fat, muscle, blood vessels, etc.); leukemias which are cancers of blood forming tissue (*e.g.*, bone marrow tissue); lymphomas and myelomas which are cancers of immune cells; and central nervous system cancers which include cancers from brain and spinal tissue. “Cancer(s) and” “neoplasm(s)” are used herein interchangeably. As used herein, “cancer” refers to all types of cancer or neoplasm or malignant tumors including leukemias, carcinomas and sarcomas, whether new or recurring. Specific examples of cancers are: carcinomas, sarcomas, myelomas, leukemias, lymphomas and mixed type tumors. Non-limiting examples of cancers are new or recurring cancers of the brain, melanoma, bladder, breast, cervix, colon, head and neck, kidney, lung, non-small cell lung, mesothelioma, ovary, prostate, sarcoma, stomach, uterus and medulloblastoma. In some embodiments, the cancer comprises a solid tumor. In some embodiments, the cancer comprises a metastasis.

[1396] A “carbohydrate” refers to a sugar or polymer of sugars. The terms “saccharide,” “polysaccharide,” “carbohydrate,” and “oligosaccharide” may be used interchangeably. Most carbohydrates are aldehydes or ketones with many hydroxyl groups, usually one on each carbon atom of the molecule. Carbohydrates generally have the molecular formula $C_nH_{2n}O_n$. A carbohydrate may be a monosaccharide, a disaccharide, trisaccharide, oligosaccharide, or polysaccharide. The most basic carbohydrate is a monosaccharide, such as glucose, sucrose, galactose, mannose, ribose, arabinose, xylose, and fructose. Disaccharides are two joined monosaccharides. Exemplary disaccharides include sucrose, maltose, cellobiose, and lactose. Typically, an oligosaccharide includes between three and six monosaccharide units (*e.g.*, raffinose, stachyose), and polysaccharides include six or more monosaccharide units. Exemplary polysaccharides include starch, glycogen, and cellulose. Carbohydrates may contain modified saccharide units such as 2'-deoxyribose wherein a hydroxyl group is removed, 2'-fluororibose wherein a hydroxyl group is replaced with a fluorine, or N-acetylglucosamine, a nitrogen-containing form of glucose (*e.g.*, 2'-fluororibose, deoxyribose, and hexose). Carbohydrates may exist in many different forms, for example, conformers, cyclic forms, acyclic forms, stereoisomers, tautomers, anomers, and isomers.

[1397] “Cellular augmentation” broadly refers to the influx of cells or expansion of cells in an environment that are not substantially present in the environment prior to administration of a composition and not present in the composition itself. Cells that

augment the environment include immune cells, stromal cells, bacterial and fungal cells. Environments of particular interest are the microenvironments where cancer cells reside or locate. In some instances, the microenvironment is a tumor microenvironment or a tumor draining lymph node. In other instances, the microenvironment is a pre-cancerous tissue site or the site of local administration of a composition or a site where the composition will accumulate after remote administration.

[1398] “Clade” refers to the OTUs or members of a phylogenetic tree that are downstream of a statistically valid node in a phylogenetic tree. The clade comprises a set of terminal leaves in the phylogenetic tree that is a distinct monophyletic evolutionary unit and that share some extent of sequence similarity.

[1399] A “combination” of bacteria from two or more strains includes the physical co-existence of the bacteria, either in the same material or product or in physically connected products, as well as the temporal co-administration or co-localization of the bacteria from the two or more strains.

[1400] A “combination” of mEVs (such as smEVs and/or pmEVs) from two or more microbial (such as bacteria) strains includes the physical co-existence of the microbes from which the mEVs (such as smEVs and/or pmEVs) are obtained, either in the same material or product or in physically connected products, as well as the temporal co-administration or co-localization of the mEVs (such as smEVs and/or pmEVs) from the two or more strains.

[1401] The term “decrease” or “deplete” means a change, such that the difference is, depending on circumstances, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 1/100, 1/1000, 1/10,000, 1/100,000, 1/1,000,000 or undetectable after treatment when compared to a pre-treatment state. Properties that may be decreased include the number of immune cells, bacterial cells, stromal cells, myeloid derived suppressor cells, fibroblasts, metabolites; the level of a cytokine; or another physical parameter (such as ear thickness (e.g., in a DTH animal model) or tumor size).

[1402] “Dysbiosis” refers to a state of the microbiota or microbiome of the gut or other body area, including, e.g., mucosal or skin surfaces (or any other microbiome niche) in which the normal diversity and/or function of the host gut microbiome ecological networks (“microbiome”) are disrupted. A state of dysbiosis may result in a diseased state, or it may be unhealthy under only certain conditions or only if present for a prolonged period. Dysbiosis may be due to a variety of factors, including, environmental factors,

infectious agents, host genotype, host diet and/or stress. A dysbiosis may result in: a change (e.g., increase or decrease) in the prevalence of one or more bacteria types (e.g., anaerobic), species and/or strains, change (e.g., increase or decrease) in diversity of the host microbiome population composition; a change (e.g., increase or reduction) of one or more populations of symbiont organisms resulting in a reduction or loss of one or more beneficial effects; overgrowth of one or more populations of pathogens (e.g., pathogenic bacteria); and/or the presence of, and/or overgrowth of, symbiotic organisms that cause disease only when certain conditions are present.

[1403] The term “ecological consortium” is a group of bacteria which trades metabolites and positively co-regulates one another, in contrast to two bacteria which induce host synergy through activating complementary host pathways for improved efficacy.

[1404] The term “effective dose” or “effective amount” is an amount of a pharmaceutical agent that is effective to achieve a desired therapeutic response in a subject for a particular agent, composition, and mode of administration.

[1405] As used herein, “engineered bacteria” are any bacteria that have been genetically altered from their natural state by human activities, and the progeny of any such bacteria. Engineered bacteria include, for example, the products of targeted genetic modification, the products of random mutagenesis screens and the products of directed evolution.

[1406] The term “epitope” means a protein determinant capable of specific binding to an antibody or T cell receptor. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains. Certain epitopes can be defined by a particular sequence of amino acids to which an antibody is capable of binding.

[1407] The term “gene” is used broadly to refer to any nucleic acid associated with a biological function. The term “gene” applies to a specific genomic sequence, as well as to a cDNA or an mRNA encoded by that genomic sequence.

[1408] “Identity” as between nucleic acid sequences of two nucleic acid molecules can be determined as a percentage of identity using known computer algorithms such as the “FASTA” program, using for example, the default parameters as in Pearson *et al.* (1988) Proc. Natl. Acad. Sci. USA 85:2444 (other programs include the GCG program package (Devereux, J., *et al.*, Nucleic Acids Research 12(I):387 (1984)), BLASTP, BLASTN, FASTA Atschul, S. F., *et al.*, J Molec Biol 215:403 (1990); Guide to Huge Computers,

Martin J. Bishop, ed., Academic Press, San Diego, 1994, and Carillo *et al.* (1988) SIAM J Applied Math 48:1073). For example, the BLAST function of the National Center for Biotechnology Information database can be used to determine identity. Other commercially or publicly available programs include, DNASTar “MegAlign” program (Madison, Wis.) and the University of Wisconsin Genetics Computer Group (UWG) “Gap” program (Madison Wis.)).

[1409] As used herein, the term “immune disorder” refers to any disease, disorder or disease symptom caused by an activity of the immune system, including autoimmune diseases, inflammatory diseases and allergies. Immune disorders include, but are not limited to, autoimmune diseases (e.g., psoriasis, atopic dermatitis, lupus, scleroderma, hemolytic anemia, vasculitis, type one diabetes, Grave’s disease, rheumatoid arthritis, multiple sclerosis, Goodpasture’s syndrome, pernicious anemia and/or myopathy), inflammatory diseases (e.g., acne vulgaris, asthma, celiac disease, chronic prostatitis, glomerulonephritis, inflammatory bowel disease, pelvic inflammatory disease, reperfusion injury, rheumatoid arthritis, sarcoidosis, transplant rejection, vasculitis and/or interstitial cystitis), and/or an allergies (e.g., food allergies, drug allergies and/or environmental allergies).

[1410] “Immunotherapy” is treatment that uses a subject’s immune system to treat disease (e.g., immune disease, inflammatory disease, metabolic disease, cancer) and includes, for example, checkpoint inhibitors, cancer vaccines, cytokines, cell therapy, CAR-T cells, and dendritic cell therapy.

[1411] The term “increase” means a change, such that the difference is, depending on circumstances, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 2-fold, 4-fold, 10-fold, 100-fold, 10^3 fold, 10^4 fold, 10^5 fold, 10^6 fold, and/or 10^7 fold greater after treatment when compared to a pre-treatment state. Properties that may be increased include the number of immune cells, bacterial cells, stromal cells, myeloid derived suppressor cells, fibroblasts, metabolites; the level of a cytokine; or another physical parameter (such as ear thickness (e.g., in a DTH animal model) or tumor size).

[1412] “Innate immune agonists” or “immuno-adjuvants” are small molecules, proteins, or other agents that specifically target innate immune receptors including Toll-Like Receptors (TLR), NOD receptors, RLRs, C-type lectin receptors, STING-cGAS Pathway components, inflammasome complexes. For example, LPS is a TLR-4 agonist that is bacterially derived or synthesized and aluminum can be used as an immune stimulating adjuvant. immuno-adjuvants are a specific class of broader adjuvant or adjuvant therapy.

Examples of STING agonists include, but are not limited to, 2'3'-cGAMP, 3'3'-cGAMP, c-di-AMP, c-di-GMP, 2'2'-cGAMP, and 2'3'-cGAM(PS)₂ (Rp/Sp) (Rp, Sp-isomers of the bis-phosphorothioate analog of 2'3'-cGAMP). Examples of TLR agonists include, but are not limited to, TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10 and TLR11. Examples of NOD agonists include, but are not limited to, N-acetylmuramyl-L-alanyl-D-isoglutamine (muramyl dipeptide (MDP)), gamma-D-glutamyl-meso-diaminopimelic acid (iE-DAP), and desmuramylpeptides (DMP).

[1413] The “internal transcribed spacer” or “ITS” is a piece of non-functional RNA located between structural ribosomal RNAs (rRNA) on a common precursor transcript often used for identification of eukaryotic species in particular fungi. The rRNA of fungi that forms the core of the ribosome is transcribed as a single gene and consists of the 18S, 5.8S and 28S regions with ITS4 and 5 between the 18S and 5.8S and 5.8S and 28S regions, respectively. These two intergenic segments between the 18S and 5.8S and 5.8S and 28S regions are removed by splicing and contain significant variation between species for barcoding purposes as previously described (Schoch et al Nuclear ribosomal internal transcribed spacer (ITS) region as a universal DNA barcode marker for Fungi. PNAS 109:6241-6246. 2012). 18S rDNA is traditionally used for phylogenetic reconstruction however the ITS can serve this function as it is generally highly conserved but contains hypervariable regions that harbor sufficient nucleotide diversity to differentiate genera and species of most fungus.

[1414] The term “isolated” or “enriched” encompasses a microbe (such as a bacterium), an mEV (such as an smEV and/or pmEV) or other entity or substance that has been (1) separated from at least some of the components with which it was associated when initially produced (whether in nature or in an experimental setting), and/or (2) produced, prepared, purified, and/or manufactured by the hand of man. Isolated microbes or mEVs may be separated from at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or more of the other components with which they were initially associated. In some embodiments, isolated microbes or mEVs are more than about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% pure. As used herein, a substance is “pure” if it is substantially free of other components. The terms “purify,” “purifying” and “purified” refer to a microbe or other material that has been separated from at least some of the components with which it was associated either

when initially produced or generated (*e.g.*, whether in nature or in an experimental setting), or during any time after its initial production. A microbe or a microbial population or mEVs may be considered purified if it is isolated at or after production, such as from a material or environment containing the microbe or microbial population, and a purified microbe or microbial population may contain other materials up to about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or above about 90% and still be considered “isolated.” In some embodiments, purified microbes or microbial population or mEVs are more than about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% pure. In the instance of microbial compositions provided herein, the one or more microbial types present in the composition can be independently purified from one or more other microbes produced and/or present in the material or environment containing the microbial type. Microbial compositions and the microbial components thereof are generally purified from residual habitat products.

[1415] As used herein a “lipid” includes fats, oils, triglycerides, cholesterol, phospholipids, fatty acids in any form including free fatty acids. Fats, oils and fatty acids can be saturated, unsaturated (*cis* or *trans*) or partially unsaturated (*cis* or *trans*).

[1416] “Metabolite” as used herein refers to any and all molecular compounds, compositions, molecules, ions, co-factors, catalysts or nutrients used as substrates in any cellular or microbial metabolic reaction or resulting as product compounds, compositions, molecules, ions, co-factors, catalysts or nutrients from any cellular or microbial metabolic reaction.

[1417] “Microbe” refers to any natural or engineered organism characterized as an archaeon, parasite, bacterium, fungus, microscopic alga, protozoan, and the stages of development or life cycle stages (*e.g.*, vegetative, spore (including sporulation, dormancy, and germination), latent, biofilm) associated with the organism. Examples of gut microbes include: *Actinomyces graevenitzii*, *Actinomyces odontolyticus*, *Akkermansia muciniphila*, *Bacteroides caccae*, *Bacteroides fragilis*, *Bacteroides putredinis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bifidobacterium adolescentis*, *Bifidobacterium bifidum*, *Bilophila wadsworthia*, *Blautia*, *Butyrivibrio*, *Campylobacter gracilis*, *Clostridia cluster III*, *Clostridia cluster IV*, *Clostridia cluster IX* (*Acidaminococcaceae* group), *Clostridia cluster XI*, *Clostridia cluster XIII* (*Peptostreptococcus* group), *Clostridia cluster XIV*, *Clostridia cluster XV*, *Collinsella aerofaciens*, *Coprococcus*, *Corynebacterium*

sunsvallense, *Desulfomonas pigra*, *Dorea formicigenerans*, *Dorea longicatena*, *Escherichia coli*, *Eubacterium hadrum*, *Eubacterium rectale*, *Faecalibacteria prausnitzii*, *Gemella*, *Lactococcus*, *Lachnospira*, *Mollicutes cluster XVI*, *Mollicutes cluster XVIII*, *Prevotella*, *Rothia mucilaginosa*, *Ruminococcus callidus*, *Ruminococcus gnavus*, *Ruminococcus torques*, and *Streptococcus*.

[1418] “Microbial extracellular vesicles” (mEVs) can be obtained from microbes such as bacteria, archaea, fungi, microscopic algae, protozoans, and parasites. In some embodiments, the mEVs are obtained from bacteria. mEVs include secreted microbial extracellular vesicles (smEVs) and processed microbial extracellular vesicles (pmEVs). “Secreted microbial extracellular vesicles” (smEVs) are naturally-produced vesicles derived from microbes. smEVs are comprised of microbial lipids and/or microbial proteins and/or microbial nucleic acids and/or microbial carbohydrate moieties, and are isolated from culture supernatant. The natural production of these vesicles can be artificially enhanced (e.g., increased) or decreased through manipulation of the environment in which the bacterial cells are being cultured (e.g., by media or temperature alterations). Further, smEV compositions may be modified to reduce, increase, add, or remove microbial components or foreign substances to alter efficacy, immune stimulation, stability, immune stimulatory capacity, stability, organ targeting (e.g., lymph node), absorption (e.g., gastrointestinal), and/or yield (e.g., thereby altering the efficacy). As used herein, the term “purified smEV composition” or “smEV composition” refers to a preparation of smEVs that have been separated from at least one associated substance found in a source material (e.g., separated from at least one other microbial component) or any material associated with the smEVs in any process used to produce the preparation. It can also refer to a composition that has been significantly enriched for specific components. “Processed microbial extracellular vesicles” (pmEVs) are a non-naturally-occurring collection of microbial membrane components that have been purified from artificially lysed microbes (e.g., bacteria) (e.g., microbial membrane components that have been separated from other, intracellular microbial cell components), and which may comprise particles of a varied or a selected size range, depending on the method of purification. A pool of pmEVs is obtained by chemically disrupting (e.g., by lysozyme and/or lysostaphin) and/or physically disrupting (e.g., by mechanical force) microbial cells and separating the microbial membrane components from the intracellular components through centrifugation and/or ultracentrifugation, or other methods. The resulting pmEV mixture contains an enrichment of the microbial membranes

and the components thereof (e.g., peripherally associated or integral membrane proteins, lipids, glycans, polysaccharides, carbohydrates, other polymers), such that there is an increased concentration of microbial membrane components, and a decreased concentration (e.g., dilution) of intracellular contents, relative to whole microbes. For gram-positive bacteria, pmEVs may include cell or cytoplasmic membranes. For gram-negative bacteria, a pmEV may include inner and outer membranes. pmEVs may be modified to increase purity, to adjust the size of particles in the composition, and/or modified to reduce, increase, add or remove, microbial components or foreign substances to alter efficacy, immune stimulation, stability, immune stimulatory capacity, stability, organ targeting (e.g., lymph node), absorption (e.g., gastrointestinal), and/or yield (e.g., thereby altering the efficacy). pmEVs can be modified by adding, removing, enriching for, or diluting specific components, including intracellular components from the same or other microbes. As used herein, the term “purified pmEV composition” or “pmEV composition” refers to a preparation of pmEVs that have been separated from at least one associated substance found in a source material (e.g., separated from at least one other microbial component) or any material associated with the pmEVs in any process used to produce the preparation. It can also refer to a composition that has been significantly enriched for specific components.

[1419] “Microbiome” broadly refers to the microbes residing on or in body site of a subject or patient. Microbes in a microbiome may include bacteria, viruses, eukaryotic microorganisms, and/or viruses. Individual microbes in a microbiome may be metabolically active, dormant, latent, or exist as spores, may exist planktonically or in biofilms, or may be present in the microbiome in sustainable or transient manner. The microbiome may be a commensal or healthy-state microbiome or a disease-state or dysbiotic microbiome. The microbiome may be native to the subject or patient, or components of the microbiome may be modulated, introduced, or depleted due to changes in health state (e.g., precancerous or cancerous state) or treatment conditions (e.g., antibiotic treatment, exposure to different microbes). In some aspects, the microbiome occurs at a mucosal surface. In some aspects, the microbiome is a gut microbiome. In some aspects, the microbiome is a tumor microbiome.

[1420] A “microbiome profile” or a “microbiome signature” of a tissue or sample refers to an at least partial characterization of the bacterial makeup of a microbiome. In some embodiments, a microbiome profile indicates whether at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 or more bacterial

strains are present or absent in a microbiome. In some embodiments, a microbiome profile indicates whether at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 or more cancer-associated bacterial strains are present in a sample. In some embodiments, the microbiome profile indicates the relative or absolute amount of each bacterial strain detected in the sample. In some embodiments, the microbiome profile is a cancer-associated microbiome profile. A cancer-associated microbiome profile is a microbiome profile that occurs with greater frequency in a subject who has cancer than in the general population. In some embodiments, the cancer-associated microbiome profile comprises a greater number of or amount of cancer-associated bacteria than is normally present in a microbiome of an otherwise equivalent tissue or sample taken from an individual who does not have cancer.

[1421] “Modified” in reference to a bacteria broadly refers to a bacteria that has undergone a change from its wild-type form. Bacterial modification can result from engineering bacteria. Examples of bacterial modifications include genetic modification, gene expression modification, phenotype modification, formulation modification, chemical modification, and dose or concentration. Examples of improved properties are described throughout this specification and include, e.g., attenuation, auxotrophy, homing, or antigenicity. Phenotype modification might include, by way of example, bacteria growth in media that modify the phenotype of a bacterium such that it increases or decreases virulence.

[1422] An “oncobiome” as used herein comprises tumorigenic and/or cancer-associated microbiota, wherein the microbiota comprises one or more of a virus, a bacterium, a fungus, a protist, a parasite, or another microbe.

[1423] “Oncotrophic” or “oncophilic” microbes and bacteria are microbes that are highly associated or present in a cancer microenvironment. They may be preferentially selected for within the environment, preferentially grow in a cancer microenvironment or hone to a said environment.

[1424] “Operational taxonomic units” and “OTU(s)” refer to a terminal leaf in a phylogenetic tree and is defined by a nucleic acid sequence, e.g., the entire genome, or a specific genetic sequence, and all sequences that share sequence identity to this nucleic acid sequence at the level of species. In some embodiments the specific genetic sequence may be the 16S sequence or a portion of the 16S sequence. In other embodiments, the entire genomes of two entities are sequenced and compared. In another embodiment, select

regions such as multilocus sequence tags (MLST), specific genes, or sets of genes may be genetically compared. For 16S, OTUs that share $\geq 97\%$ average nucleotide identity across the entire 16S or some variable region of the 16S are considered the same OTU. See e.g., Claesson MJ, Wang Q, O'Sullivan O, Greene-Diniz R, Cole JR, Ross RP, and O'Toole PW. 2010. Comparison of two next-generation sequencing technologies for resolving highly complex microbiota composition using tandem variable 16S rRNA gene regions. *Nucleic Acids Res* 38: e200. Konstantinidis KT, Ramette A, and Tiedje JM. 2006. The bacterial species definition in the genomic era. *Philos Trans R Soc Lond B Biol Sci* 361: 1929–1940. For complete genomes, MLSTs, specific genes, other than 16S, or sets of genes OTUs that share $\geq 95\%$ average nucleotide identity are considered the same OTU. See e.g., Achtman M, and Wagner M. 2008. Microbial diversity and the genetic nature of microbial species. *Nat. Rev. Microbiol.* 6: 431–440. Konstantinidis KT, Ramette A, and Tiedje JM. 2006. The bacterial species definition in the genomic era. *Philos Trans R Soc Lond B Biol Sci* 361: 1929–1940. OTUs are frequently defined by comparing sequences between organisms. Generally, sequences with less than 95% sequence identity are not considered to form part of the same OTU. OTUs may also be characterized by any combination of nucleotide markers or genes, in particular highly conserved genes (e.g., “house-keeping” genes), or a combination thereof. Operational Taxonomic Units (OTUs) with taxonomic assignments made to, e.g., genus, species, and phylogenetic clade are provided herein.

[1425] As used herein, a gene is “overexpressed” in a bacteria if it is expressed at a higher level in an engineered bacteria under at least some conditions than it is expressed by a wild-type bacteria of the same species under the same conditions. Similarly, a gene is “underexpressed” in a bacteria if it is expressed at a lower level in an engineered bacteria under at least some conditions than it is expressed by a wild-type bacteria of the same species under the same conditions.

[1426] The terms “polynucleotide”, and “nucleic acid” are used interchangeably. They refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. Polynucleotides may have any three-dimensional structure, and may perform any function. The following are non-limiting examples of polynucleotides: coding or non-coding regions of a gene or gene fragment, loci (locus) defined from linkage analysis, exons, introns, messenger RNA (mRNA), micro RNA (miRNA), silencing RNA (siRNA), transfer RNA, ribosomal RNA, ribozymes, cDNA, recombinant polynucleotides, branched polynucleotides, plasmids, vectors, isolated DNA of

any sequence, isolated RNA of any sequence, nucleic acid probes, and primers. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs. If present, modifications to the nucleotide structure may be imparted before or after assembly of the polymer. A polynucleotide may be further modified, such as by conjugation with a labeling component. In all nucleic acid sequences provided herein, U nucleotides are interchangeable with T nucleotides.

[1427] As used herein, the term “preventing” a disease or condition in a subject refers to administering to the subject to a pharmaceutical treatment, e.g., the administration of one or more agents (e.g., pharmaceutical agent), such that onset of at least one symptom of the disease or condition is delayed or prevented.

[1428] As used herein, a substance is “pure” if it is substantially free of other components. The terms “purify,” “purifying” and “purified” refer to an mEV (such as an smEV and/or a pmEV) preparation or other material that has been separated from at least some of the components with which it was associated either when initially produced or generated (e.g., whether in nature or in an experimental setting), or during any time after its initial production. An mEV (such as an smEV and/or a pmEV) preparation or compositions may be considered purified if it is isolated at or after production, such as from one or more other bacterial components, and a purified microbe or microbial population may contain other materials up to about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or above about 90% and still be considered “purified.” In some embodiments, purified mEVs (such as smEVs and/or pmEVs) are more than about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% pure. mEV (such as an smEV and/or a pmEV) compositions (or preparations) are, e.g., purified from residual habitat products.

[1429] As used herein, the term “purified mEV composition” or “mEV composition” refers to a preparation that includes mEVs (such as smEVs and/or pmEVs) that have been separated from at least one associated substance found in a source material (e.g., separated from at least one other bacterial component) or any material associated with the mEVs (such as smEVs and/or pmEVs) in any process used to produce the preparation. It also refers to a composition that has been significantly enriched or concentrated. In some embodiments, the mEVs (such as smEVs and/or pmEVs) are concentrated by 2 fold, 3-fold, 4-fold, 5-fold, 10-fold, 100-fold, 1000-fold, 10,000-fold or more than 10,000 fold.

[1430] “Residual habitat products” refers to material derived from the habitat for microbiota within or on a subject. For example, fermentation cultures of microbes can contain contaminants, e.g., other microbe strains or forms (e.g., bacteria, virus, mycoplasma, and/or fungus). For example, microbes live in feces in the gastrointestinal tract, on the skin itself, in saliva, mucus of the respiratory tract, or secretions of the genitourinary tract (i.e., biological matter associated with the microbial community). Substantially free of residual habitat products means that the microbial composition no longer contains the biological matter associated with the microbial environment on or in the culture or human or animal subject and is 100% free, 99% free, 98% free, 97% free, 96% free, or 95% free of any contaminating biological matter associated with the microbial community. Residual habitat products can include abiotic materials (including undigested food) or it can include unwanted microorganisms. Substantially free of residual habitat products may also mean that the microbial composition contains no detectable cells from a culture contaminant or a human or animal and that only microbial cells are detectable. In one embodiment, substantially free of residual habitat products may also mean that the microbial composition contains no detectable viral (including bacteria, viruses (e.g., phage)), fungal, mycoplasmal contaminants. In another embodiment, it means that fewer than $1 \times 10^{-20}\%$, $1 \times 10^{-30}\%$, $1 \times 10^{-40}\%$, $1 \times 10^{-50}\%$, $1 \times 10^{-60}\%$, $1 \times 10^{-70}\%$, $1 \times 10^{-80}\%$ of the viable cells in the microbial composition are human or animal, as compared to microbial cells. There are multiple ways to accomplish this degree of purity, none of which are limiting. Thus, contamination may be reduced by isolating desired constituents through multiple steps of streaking to single colonies on solid media until replicate (such as, but not limited to, two) streaks from serial single colonies have shown only a single colony morphology. Alternatively, reduction of contamination can be accomplished by multiple rounds of serial dilutions to single desired cells (e.g., a dilution of 10^{-8} or 10^{-9}), such as through multiple 10-fold serial dilutions. This can further be confirmed by showing that multiple isolated colonies have similar cell shapes and Gram staining behavior. Other methods for confirming adequate purity include genetic analysis (e.g., PCR, DNA sequencing), serology and antigen analysis, enzymatic and metabolic analysis, and methods using instrumentation such as flow cytometry with reagents that distinguish desired constituents from contaminants.

[1431] As used herein, “specific binding” refers to the ability of an antibody to bind to a predetermined antigen or the ability of a polypeptide to bind to its predetermined binding partner. Typically, an antibody or polypeptide specifically binds to its

predetermined antigen or binding partner with an affinity corresponding to a K_D of about 10^{-7} M or less, and binds to the predetermined antigen/binding partner with an affinity (as expressed by K_D) that is at least 10 fold less, at least 100 fold less or at least 1000 fold less than its affinity for binding to a non-specific and unrelated antigen/binding partner (e.g., BSA, casein). Alternatively, specific binding applies more broadly to a two-component system where one component is a protein, lipid, or carbohydrate or combination thereof and engages with the second component which is a protein, lipid, carbohydrate or combination thereof in a specific way.

[1432] “Strain” refers to a member of a bacterial species with a genetic signature such that it may be differentiated from closely-related members of the same bacterial species. The genetic signature may be the absence of all or part of at least one gene, the absence of all or part of at least one regulatory region (e.g., a promoter, a terminator, a riboswitch, a ribosome binding site), the absence (“curing”) of at least one native plasmid, the presence of at least one recombinant gene, the presence of at least one mutated gene, the presence of at least one foreign gene (a gene derived from another species), the presence at least one mutated regulatory region (e.g., a promoter, a terminator, a riboswitch, a ribosome binding site), the presence of at least one non-native plasmid, the presence of at least one antibiotic resistance cassette, or a combination thereof. Genetic signatures between different strains may be identified by PCR amplification optionally followed by DNA sequencing of the genomic region(s) of interest or of the whole genome. In the case in which one strain (compared with another of the same species) has gained or lost antibiotic resistance or gained or lost a biosynthetic capability (such as an auxotrophic strain), strains may be differentiated by selection or counter-selection using an antibiotic or nutrient/metabolite, respectively.

[1433] The terms “subject” or “patient” refers to any mammal. A subject or a patient described as “in need thereof” refers to one in need of a treatment (or prevention) for a disease. Mammals (i.e., mammalian animals) include humans, laboratory animals (e.g., primates, rats, mice), livestock (e.g., cows, sheep, goats, pigs), and household pets (e.g., dogs, cats, rodents). The subject may be a human. The subject may be a non-human mammal including but not limited to of a dog, a cat, a cow, a horse, a pig, a donkey, a goat, a camel, a mouse, a rat, a guinea pig, a sheep, a llama, a monkey, a gorilla or a chimpanzee. The subject may be healthy, or may be suffering from a cancer at any developmental stage, wherein any of the stages are either caused by or opportunistically supported of a cancer

associated or causative pathogen, or may be at risk of developing a cancer, or transmitting to others a cancer associated or cancer causative pathogen. In some embodiments, a subject has lung cancer, bladder cancer, prostate cancer, plasmacytoma, colorectal cancer, rectal cancer, Merkel Cell carcinoma, salivary gland carcinoma, ovarian cancer, and/or melanoma. The subject may have a tumor. The subject may have a tumor that shows enhanced macropinocytosis with the underlying genomics of this process including Ras activation. In other embodiments, the subject has another cancer. In some embodiments, the subject has undergone a cancer therapy.

[1434] As used herein, a “systemic effect” in a subject treated with a pharmaceutical composition containing bacteria or mEVs (e.g., a pharmaceutical agent comprising bacteria or mEVs) of the instant invention means a physiological effect occurring at one or more sites outside the gastrointestinal tract. Systemic effect(s) can result from immune modulation (e.g., via an increase and/or a reduction of one or more immune cell types or subtypes (e.g., CD8+ T cells) and/or one or more cytokines). Such systemic effect(s) may be the result of the modulation by bacteria or mEVs of the instant invention on immune or other cells (such as epithelial cells) in the gastrointestinal tract which then, directly or indirectly, result in the alteration of activity (activation and/or deactivation) of one or more biochemical pathways outside the gastrointestinal tract. The systemic effect may include treating or preventing a disease or condition in a subject.

[1435] As used herein, the term “treating” a disease in a subject or “treating” a subject having or suspected of having a disease refers to administering to the subject to a pharmaceutical treatment, e.g., the administration of one or more agents (e.g., pharmaceutical agent), such that at least one symptom of the disease is decreased or prevented from worsening. Thus, in one embodiment, “treating” refers inter alia to delaying progression, expediting remission, inducing remission, augmenting remission, speeding recovery, increasing efficacy of or decreasing resistance to alternative therapeutics, or a combination thereof.

[1436] As used herein, a “type” of bacteria may be distinguished from other bacteria by: genus, species, sub-species, strain or by any other taxonomic categorization, whether based on morphology, physiology, genotype, protein expression or other characteristics known in the art.

Bacteria

[1437] In certain aspects, the pharmaceutical agent of the solid dosage forms described herein comprises bacteria and/or microbial extracellular vesicles (mEVs) (such as smEVs and/or pmEVs). Within a pharmaceutical agent that contains bacteria and mEVs, the mEVs can be from the same bacterial origin (e.g., same strain) as the bacteria of the pharmaceutical agent. The pharmaceutical agent can contain bacteria and/or mEVs from one or more strains.

[1438] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are modified to reduce toxicity or other adverse effects, to enhance delivery) (e.g., oral delivery) (e.g., by improving acid resistance, muco-adherence and/or penetration and/or resistance to bile acids, digestive enzymes, resistance to anti-microbial peptides and/or antibody neutralization), to target desired cell types (e.g., M-cells, goblet cells, enterocytes, dendritic cells, macrophages), to enhance their immunomodulatory and/or therapeutic effect of the bacteria and/or mEVs (e.g., either alone or in combination with another pharmaceutical agent), and/or to enhance immune activation or suppression by the bacteria and/or mEVs (such as smEVs and/or pmEVs) (e.g., through modified production of polysaccharides, pili, fimbriae, adhesins). In some embodiments, the engineered bacteria described herein are modified to improve bacteria and/or mEV (such as smEV and/or pmEV) manufacturing (e.g., higher oxygen tolerance, stability, improved freeze-thaw tolerance, shorter generation times). For example, in some embodiments, the engineered bacteria described include bacteria harboring one or more genetic changes, such change being an insertion, deletion, translocation, or substitution, or any combination thereof, of one or more nucleotides contained on the bacterial chromosome or endogenous plasmid and/or one or more foreign plasmids, wherein the genetic change may result in the overexpression and/or underexpression of one or more genes. The engineered bacteria may be produced using any technique known in the art, including but not limited to site-directed mutagenesis, transposon mutagenesis, knock-outs, knock-ins, polymerase chain reaction mutagenesis, chemical mutagenesis, ultraviolet light mutagenesis, transformation (chemically or by electroporation), phage transduction, directed evolution, or any combination thereof.

[1439] Examples of taxonomic groups (e.g., class, order, family, genus, species or strain) of bacteria that can be used as a source of bacteria and/or mEVs (such as smEVs and/or pmEVs) for a pharmaceutical agent described herein are provided herein (e.g., listed

in Table 1, Table 2, and/or Table 3 and/or elsewhere in the specification (e.g., Table J)). In some embodiments, the bacterial strain is a bacterial strain having a genome that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8% or 99.9% sequence identity to a strain listed herein. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are oncotrophic bacteria. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are immunomodulatory bacteria. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are immunostimulatory bacteria. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are immunosuppressive bacteria. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are immunomodulatory bacteria. In certain embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are generated from a combination of bacterial strains provided herein. In some embodiments, the combination is a combination of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45 or 50 bacterial strains. In some embodiments, the combination includes the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are from bacterial strains listed herein and/or bacterial strains having a genome that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8% or 99.9% sequence identity to a strain listed herein (e.g., listed in Table 1, Table 2, and/or Table 3 and/or elsewhere in the specification (e.g., Table J)). In certain embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are generated from a bacterial strain provided herein. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are from a bacterial strain listed herein (e.g., listed in Table 1, Table 2, and/or Table 3 and/or elsewhere in the specification (e.g., Table J)) and/or a bacterial strain having a genome that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8% or 99.9% sequence identity to a strain listed herein (e.g., listed in Table 1, Table 2, and/or Table 3 and/or elsewhere in the specification (e.g., Table J)).

[1440] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are Gram negative bacteria.

[1441] In some embodiments, the Gram negative bacteria belong to the class *Negativicutes*. The *Negativicutes* represent a unique class of microorganisms as they are the only diderm members of the *Firmicutes* phylum. These anaerobic organisms can be found in the environment and are normal commensals of the oral cavity and GI tract of humans. Because these organisms have an outer membrane, the yields of EVs from this class were investigated. It was found that on a per cell basis these bacteria produce a high number of vesicles (10-150 EVs/cell). The EVs from these organisms are broadly stimulatory and highly potent in *in vitro* assays. Investigations into their therapeutic applications in several oncology and inflammation *in vivo* models have shown their therapeutic potential. The *Negativicutes* class includes the families *Veillonellaceae*, *Selenomonadaceae*, *Acidaminococcaceae*, and *Sporomusaceae*. The *Negativicutes* class includes the genera *Megasphaera*, *Selenomonas*, *Propionospora*, and *Acidaminococcus*. Exemplary *Negativicutes* species include, but are not limited to, *Megasphaera sp.*, *Selenomonas felix*, *Acidaminococcus intestine*, and *Propionospora sp.*

[1442] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are Gram positive bacteria.

[1443] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are aerobic bacteria.

[1444] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are anaerobic bacteria. In some embodiments, the anaerobic bacteria comprise obligate anaerobes. In some embodiments, the anaerobic bacteria comprise facultative anaerobes.

[1445] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are acidophile bacteria.

[1446] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are alkaliphile bacteria.

[1447] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are neutralophile bacteria.

[1448] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are fastidious bacteria.

[1449] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are nonfastidious bacteria.

[1450] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained or the mEVs themselves are lyophilized.

[1451] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained or the mEVs themselves are gamma irradiated (e.g., at 17.5 or 25 kGy).

[1452] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained or the mEVs themselves are UV irradiated.

[1453] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained or the mEVs themselves are heat inactivated (e.g., at 50°C for two hours or at 90°C for two hours).

[1454] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained or the mEVs themselves are acid treated.

[1455] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained or the mEVs themselves are oxygen sparged (e.g., at 0.1 vvm for two hours).

[1456] The phase of growth can affect the amount or properties of bacteria and/or mEVs produced by bacteria. For example, in the methods of mEVs preparation provided herein, mEVs can be isolated, e.g., from a culture, at the start of the log phase of growth, midway through the log phase, and/or once stationary phase growth has been reached.

[1457] In certain embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained from obligate anaerobic bacteria. Examples of obligate anaerobic bacteria include gram-negative rods (including the genera of *Bacteroides*, *Prevotella*, *Porphyromonas*, *Fusobacterium*, *Bilophila* and *Sutterella spp.*), gram-positive cocci (primarily *Peptostreptococcus spp.*), gram-positive spore-forming (*Clostridium spp.*), non-spore-forming bacilli (*Actinomyces*, *Propionibacterium*, *Eubacterium*, *Lactobacillus* and *Bifidobacterium spp.*), and gram-negative cocci (mainly *Veillonella spp.*). In some embodiments, the obligate anaerobic bacteria are of a genus

selected from the group consisting of *Agathobaculum*, *Atopobium*, *Blautia*, *Burkholderia*, *Dielma*, *Longicatena*, *Paraclostridium*, *Turicibacter*, and *Tyzzerella*.

[1458] The *Negativicutes* class includes the families *Veillonellaceae*, *Selenomonadaceae*, *Acidaminococcaceae*, and *Sporomusaceae*. The *Negativicutes* class includes the genera *Megasphaera*, *Selenomonas*, *Propionospora*, and *Acidaminococcus*. Exemplary *Negativicutes* species include, but are not limited to, *Megasphaera* sp., *Selenomonas felix*, *Acidaminococcus intestini*, and *Propionospora* sp.

[1459] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Negativicutes* class.

[1460] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Veillonellaceae* family.

[1461] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Selenomonadaceae* family.

[1462] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Acidaminococcaceae* family.

[1463] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Sporomusaceae* family.

[1464] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Megasphaera* genus.

[1465] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Selenomonas* genus.

[1466] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Propionospora* genus.

[1467] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Acidaminococcus* genus.

[1468] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Megasphaera* sp. bacteria.

[1469] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Selenomonas felix* bacteria.

[1470] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Acidaminococcus intestini* bacteria.

[1471] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Propionospora sp.* bacteria.

[1472] The *Oscillospiraceae* family within the *Clostridia* class of microorganisms are common commensal organisms of vertebrates.

[1473] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Clostridia* class.

[1474] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Oscillospiraceae* family.

[1475] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Faecalibacterium* genus.

[1476] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Fournierella* genus.

[1477] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Harryflintia* genus.

[1478] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Agathobaculum* genus.

[1479] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Faecalibacterium prausnitzii* (e.g., *Faecalibacterium prausnitzii* Strain A) bacteria.

[1480] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Fournierella massiliensis* (e.g., *Fournierella massiliensis* Strain A) bacteria.

[1481] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Harryflintia acetispora* (e.g., *Harryflintia acetispora* Strain A) bacteria.

[1482] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Agathobaculum sp.* (e.g., *Agathobaculum sp.* Strain A) bacteria.

[1483] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are bacteria of a genus selected from the group consisting of *Escherichia*, *Klebsiella*, *Lactobacillus*, *Shigella*, and *Staphylococcus*.

[1484] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are a species selected from the group consisting of *Blautia massiliensis*, *Paraclostridium benzoelyticum*, *Dielma fastidiosa*, *Longicatena caecimuris*, *Lactococcus lactis cremoris*, *Tyzzera nexilis*, *Hungatella effluvia*, *Klebsiella quasipneumoniae subsp. Similipneumoniae*, *Klebsiella oxytoca*, and *Veillonella tobetsuensis*.

[1485] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are a *Prevotella* bacteria selected from the group consisting of *Prevotella albensis*, *Prevotella amnii*, *Prevotella bergensis*, *Prevotella bivia*, *Prevotella brevis*, *Prevotella bryantii*, *Prevotella buccae*, *Prevotella buccalis*, *Prevotella copri*, *Prevotella dentalis*, *Prevotella denticola*, *Prevotella disiens*, *Prevotella histicola*, *Prevotella intermedia*, *Prevotella maculosa*, *Prevotella marshii*, *Prevotella melaninogenica*, *Prevotella micans*, *Prevotella multiformis*, *Prevotella nigrescens*, *Prevotella oralis*, *Prevotella oris*, *Prevotella outorum*, *Prevotella pallens*, *Prevotella salivae*, *Prevotella stercorea*, *Prevotella tanneriae*, *Prevotella timonensis*, *Prevotella jejuni*, *Prevotella aurantiaca*, *Prevotella baroniae*, *Prevotella colorans*, *Prevotella corporis*, *Prevotella dentasini*, *Prevotella enoeca*, *Prevotella falsenii*, *Prevotella fusca*, *Prevotella heparinolytica*, *Prevotella loescheii*, *Prevotella multisaccharivorax*, *Prevotella nanceiensis*, *Prevotella oryzae*, *Prevotella paludivivens*, *Prevotella pleuritidis*, *Prevotella ruminicola*, *Prevotella saccharolytica*, *Prevotella scopos*, *Prevotella shahii*, *Prevotella zoogloformans*, and *Prevotella veroralis*.

[1486] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are a strain of bacteria comprising a genomic sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity (e.g., at least 99.5% sequence identity, at least 99.6% sequence identity, at least 99.7% sequence identity, at least 99.8% sequence identity, at least 99.9% sequence identity) to the genomic sequence of the strain of bacteria deposited with the ATCC Deposit number as provided in Table 3. In some embodiments, the bacteria of the pharmaceutical

agent or from which the mEVs of the pharmaceutical agent are obtained are a strain of bacteria comprising a 16S sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity (e.g., at least 99.5% sequence identity, at least 99.6% sequence identity, at least 99.7% sequence identity, at least 99.8% sequence identity, at least 99.9% sequence identity) to the 16S sequence of the strain of bacteria deposited with the ATCC Deposit number as provided in Table 3.

[1487] The *Negativicutes* class includes the families *Veillonellaceae*, *Selenomonadaceae*, *Acidaminococcaceae*, and *Sporomusaceae*. The *Negativicutes* class includes the genera *Megasphaera*, *Selenomonas*, *Propionospora*, and *Acidaminococcus*. Exemplary *Negativicutes* species include, but are not limited to, *Megasphaera* sp., *Selenomonas felix*, *Acidaminococcus intestini*, and *Propionospora* sp.

[1488] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Negativicutes* class.

[1489] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Veillonellaceae* family.

[1490] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Selenomonadaceae* family.

[1491] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Acidaminococcaceae* family.

[1492] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Sporomusaceae* family.

[1493] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Megasphaera* genus.

[1494] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Selenomonas* genus.

[1495] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Propionospora* genus.

[1496] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Acidaminococcus* genus.

[1497] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Megasphaera sp.* bacteria.

[1498] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Selenomonas felix* bacteria.

[1499] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Acidaminococcus intestini* bacteria.

[1500] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Propionospora sp.* bacteria.

[1501] The *Oscillospiraceae* family within the *Clostridia* class of microorganisms are common commensal organisms of vertebrates.

[1502] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Clostridia* class.

[1503] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Oscillospiraceae* family.

[1504] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Faecalibacterium* genus.

[1505] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Fournierella* genus.

[1506] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Harryflintia* genus.

[1507] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the *Agathobaculum* genus.

[1508] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Faecalibacterium prausnitzii* (e.g., *Faecalibacterium prausnitzii* Strain A) bacteria.

[1509] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Fournierella massiliensis* (e.g., *Fournierella massiliensis* Strain A) bacteria.

[1510] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Harryflintia acetispora* (e.g., *Harryflintia acetispora* Strain A) bacteria.

[1511] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Agathobaculum sp.* (e.g., *Agathobaculum sp.* Strain A) bacteria.

[1512] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are a strain of *Agathobaculum sp.* In some embodiments, the *Agathobaculum sp.* strain is a strain comprising at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity (e.g., at least 99.5% sequence identity, at least 99.6% sequence identity, at least 99.7% sequence identity, at least 99.8% sequence identity, at least 99.9% sequence identity) to the nucleotide sequence (e.g., genomic sequence, 16S sequence, CRISPR sequence) of the *Agathobaculum sp.* Strain A (ATCC Deposit Number PTA-125892). In some embodiments, the *Agathobaculum sp.* strain is the *Agathobaculum sp.* Strain A (ATCC Deposit Number PTA-125892).

[1513] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the class *Bacteroidia* [phylum *Bacteroidota*]. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are bacteria of order *Bacteroidales*. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the family *Porphyromonadaceae*. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the family *Prevotellaceae*. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are bacteria of the class *Bacteroidia* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are bacteria of the class *Bacteroidia* that stain Gram negative. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are bacteria of the class *Bacteroidia* wherein the bacteria is diderm and the bacteria stain Gram negative.

[1514] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are bacteria of the class *Clostridia* [phylum *Firmicutes*]. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the order *Eubacteriales*. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the family *Oscillispiraceae*. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the family *Lachnospiraceae*. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the family *Peptostreptococcaceae*. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the family *Clostridiales* family XIII/ *Incertae sedis* 41. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the class *Clostridia* that stain Gram negative. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the class *Clostridia* that stain Gram positive. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram negative. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the class *Clostridia* wherein the cell envelope structure of the bacteria is monoderm and the bacteria stain Gram positive.

[1515] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the class *Negativicutes* [phylum *Firmicutes*]. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the order *Veillonellales*. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the family *Veillonelloceae*. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the order *Selenomonadales*. In some

embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are bacteria of the family *Selenomonadaceae*. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the family *Sporomusaceae*. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are the EVs are from bacteria of the class *Negativicutes* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[1516] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the class *Synergistia* [phylum *Synergistota*]. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the order *Synergistales*. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the family *Synergistaceae*. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the class *Synergistia* that stain Gram negative. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are of the class *Synergistia* wherein the cell envelope structure of the bacteria is diderm and the bacteria stain Gram negative.

[1517] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are from one strain of bacteria, e.g., a strain provided herein.

[1518] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are from one strain of bacteria (e.g., a strain provided herein) or from more than one strain provided herein.

[1519] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Lactococcus lactis cremoris*

bacteria, e.g., a strain comprising at least 90% or at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368). In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Lactococcus* bacteria, e.g., *Lactococcus lactis cremoris* Strain A (ATCC designation number PTA-125368).

[1520] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Prevotella* bacteria, e.g., a strain comprising at least 90% or at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Prevotella* Strain B 50329 (NRRL accession number B 50329). In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Prevotella* bacteria, e.g., *Prevotella* Strain B 50329 (NRRL accession number B 50329).

[1521] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Bifidobacterium* bacteria, e.g., a strain comprising at least 90% or at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Bifidobacterium* bacteria, e.g., *Bifidobacterium* bacteria deposited as ATCC designation number PTA-125097.

[1522] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Veillonella* bacteria, e.g., a strain comprising at least 90% or at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Veillonella* bacteria deposited as ATCC designation number PTA-125691. In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Veillonella* bacteria, e.g., *Veillonella* bacteria deposited as ATCC designation number PTA-125691.

[1523] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Ruminococcus gnavus* bacteria. In some embodiments, the *Ruminococcus gnavus* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation

number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695. In some embodiments, the *Ruminococcus gnavus* bacteria are *Ruminococcus gnavus* bacteria deposited as ATCC designation number PTA-126695.

[1524] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Megasphaera sp.* bacteria. In some embodiments, the *Megasphaera sp.* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some embodiments, the *Megasphaera sp.* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770. In some embodiments, the *Megasphaera sp.* bacteria are *Megasphaera sp.* bacteria deposited as ATCC designation number PTA-126770.

[1525] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Fournierella massiliensis* bacteria. In some embodiments, the *Fournierella massiliensis* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696. In some embodiments, the *Fournierella massiliensis* bacteria are *Fournierella massiliensis* bacteria deposited as ATCC designation number PTA-126696.

[1526] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are *Harryflintia acetispora* bacteria. In some embodiments, the *Harryflintia acetispora* bacteria are a strain comprising at least 90% (or at least 97%) genomic, 16S and/or CRISPR sequence identity to the nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are a strain comprising at least 99% genomic, 16S and/or CRISPR sequence identity to the

nucleotide sequence of the *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694. In some embodiments, the *Harryflintia acetispora* bacteria are *Harryflintia acetispora* bacteria deposited as ATCC designation number PTA-126694.

[1527] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are bacteria that produce metabolites, e.g., the bacteria produce butyrate, iosine, proprionate, or tryptophan metabolites.

[1528] In some embodiments, the bacteria produce butyrate. In some embodiments, the bacteria are from the genus *Blautia*; *Christensella*; *Copracoccus*; *Eubacterium*; *Lachnospiraceae*; *Megasphaera*; or *Roseburia*.

[1529] In some embodiments, the bacteria produce iosine. In some embodiments, the bacteria are from the genus *Bifidobacterium*; *Lactobacillus*; or *Olsenella*.

[1530] In some embodiments, the bacteria produce proprionate. In some embodiments, the bacteria are from the genus *Akkermansia*; *Bacteriodes*; *Dialister*; *Eubacterium*; *Megasphaera*; *Parabacteriodes*; *Prevotella*; *Ruminococcus*; or *Veillonella*.

[1531] In some embodiments, the bacteria produce tryptophan metabolites. In some embodiments, the bacteria are from the genus *Lactobacillus* or *Peptostreptococcus*.

[1532] In some embodiments, the bacteria of the pharmaceutical agent or from which the mEVs of the pharmaceutical agent are obtained are bacteria that produce inhibitors of histone deacetylase 3 (HDAC3). In some embodiments, the bacteria are from the species *Bariatricus massiliensis*, *Faecalibacterium prausnitzii*, *Megasphaera massiliensis* or *Roseburia intestinalis*.

Table 1: Bacteria by Class

Class	Order	Family	Genus	Species
<i>Actinobacter</i>	<i>Actinomycetales</i>	<i>Mycobacteriaceae</i>	<i>Mycobacterium</i>	
		<i>Streptomyacetaceae</i>	<i>Streptomyces</i>	<i>Streptomyces lividans</i> , <i>Streptomyces coelicolor</i> , <i>Streptomyces sudanesis</i> , <i>Streptomyces somaliensis</i>
	<i>Bifidobacteriales</i>	<i>Bifidobacteriaceae</i>	<i>Bifidobacterium</i>	<i>Bifidobacterium adolescentis</i> , <i>Bifidobacterium animalis</i> , <i>Bifidobacterium bifidum</i> , <i>Bifidobacterium</i>

				<i>breve</i> , <i>Bifidobacterium lactis</i> , <i>Bifidobacterium longum</i> , <i>Bifidobacterium pseudocatenulatum</i>
	<i>Coriobacteriales</i>	<i>Coriobacteriaceae</i>	<i>Collinsella</i>	<i>Collinsella aerofaciens</i>
			<i>Olsenella</i>	<i>Olsenella faecalis</i>
	<i>Propionibacteriales</i>	<i>Propionibacteraceae</i>	<i>Propionibacterium</i>	
<i>Bacilli</i>	<i>Bacillales</i>	<i>Bacillales incertae sedis family XI</i>	<i>Gemella</i>	<i>Gemella haemolysans</i> , <i>Gemella morbillorum</i>
		<i>Listeraceae</i>	<i>Listeria</i>	<i>Listeria monocytogenes</i> , <i>Listeria welshimeri</i>
	<i>Lactobacillales</i>	<i>Enterococcaceae</i>	<i>Enterococcus</i>	<i>Enterococcus durans</i> , <i>Enterococcus faecium</i> , <i>Enterococcus faecalis</i> , <i>Enterococcus gallinarum</i> , <i>Enterococcus villorum</i>
			<i>Lactobacillus</i>	<i>Lactobacillus casei</i> , <i>Lactobacillus fermentum</i> , <i>Lactococcus lactis cremoris</i> , <i>Lactobacillus mucosae</i> , <i>Lactobacillus plantarum</i> , <i>Lactobacillus reuteri</i> , <i>Lactobacillus rhamnosus</i> , <i>L. salvarius</i>
		<i>Streptococcaceae</i>	<i>Lactococcus</i>	
			<i>Staphylococcus</i>	<i>Staphylococcus aureus</i>
			<i>Streptococcus</i>	<i>Streptococcus agalactiae</i> , <i>Streptococcus aureus</i> , <i>Streptococcus australi</i> , <i>Streptococcus mutans</i> , <i>Streptococcus parasanguinis</i> , <i>Streptococcus pneumoniae</i> , <i>Streptococcus</i>

				<i>pyogenes</i> , <i>Streptococcus</i> <i>salivarius</i>
<i>Bacteriodes</i>	<i>Bacteroidales</i>	<i>Bacteriodaceae</i>	<i>Bacteriodes</i>	<i>Bacteroides caccae</i> , <i>Bacteroides</i> <i>cellulosilyticus</i> , <i>Bacteroides</i> <i>coprocola</i> , <i>Bacteroides dorei</i> , <i>Bacteroides fragilis</i> , <i>Bacteroides ovatus</i> , <i>Bacteroides</i> <i>putredinis</i> , <i>Bacteroides</i> <i>salanitronis</i> , <i>Bacteroides</i> <i>thetaiotaomicron</i> , <i>Bacteroides</i> <i>vulgatus</i>
		<i>Odoribacteraceae</i>	<i>Odoribacter</i>	<i>Odoribacter</i> <i>splanchnicus</i>
		<i>Porphyromonadaceae</i>	<i>Parabacteriodes</i>	<i>Parabacteriodes</i> <i>distasonis</i> , <i>Parabacteroides</i> <i>goldsteinii</i> , <i>P</i> <i>Parabacteriodes</i> <i>merdae</i>
			<i>Porphyromonas</i>	<i>Porphyromonas</i> <i>gingivalis</i>
		<i>Prevotellaceae</i>	<i>Prevotella</i>	<i>Prevotella</i> <i>albensis</i> , <i>Prevotella amnii</i> , <i>Prevotella</i> <i>aurantiaca</i> , <i>Prevotella</i> <i>baroniae</i> , <i>Prevotella</i> <i>bergensis</i> , <i>Prevotella bivia</i> , <i>Prevotella brevis</i> , <i>Prevotella bryantii</i> , <i>Prevotella buccae</i> , <i>Prevotella</i> <i>buccalis</i> , <i>Prevotella</i> <i>colorans</i> , <i>Prevotella</i> <i>corporis</i> , <i>Prevotella copri</i> , <i>Prevotella dentalis</i> , <i>Prevotella</i> <i>dentasini</i> , <i>Prevotella</i> <i>denticola</i> , <i>Prevotella disiens</i> , <i>Prevotella enoeca</i> , <i>Prevotella falsenii</i> , <i>Prevotella fusca</i> ,

				<i>Prevotella</i> <i>heparinolytica</i> , <i>Prevotella</i> <i>histicola</i> , <i>Prevotella</i> <i>intermedia</i> , <i>Prevotella jejuni</i> , , <i>Prevotella</i> <i>loescheii</i> , <i>Prevotella</i> <i>maculosa</i> , <i>Prevotella marshii</i> , <i>Prevotella</i> <i>melaninogenica</i> , <i>Prevotella micans</i> , <i>Prevotella</i> <i>multiformis</i> , <i>Prevotella</i> <i>multisaccharivorax</i> , <i>Prevotella</i> <i>nanceiensis</i> , <i>Prevotella</i> <i>nigrescens</i> , <i>Prevotella oralis</i> , <i>Prevotella oris</i> , , <i>Prevotella oryzae</i> , <i>Prevotella</i> <i>oulorum</i> , <i>Prevotella pallens</i> , <i>Prevotella</i> <i>paludivivens</i> , <i>Prevotella</i> <i>pleuritidis</i> <i>Prevotella</i> <i>ruminicola</i> , <i>Prevotella</i> <i>saccharolytica</i> , <i>Prevotella salivae</i> , <i>Prevotella scopos</i> , <i>Prevotella shahii</i> , <i>Prevotella</i> <i>stercorea</i> , <i>Prevotella</i> <i>tanneriae</i> , <i>Prevotella</i> <i>timonensis</i> , <i>Prevotella</i> <i>veroralis</i> , <i>Prevotella</i> <i>zooglyphiformans</i>
		<i>Rikenellaceae</i>	<i>Alistipes</i>	<i>Alistipes communis</i> , <i>Alistipes dispar</i> , <i>A.</i> <i>finnegoldii</i> , <i>Alistipes</i> <i>indistinctus</i> , <i>Alistipes ihumii</i> , <i>Alistipes inops</i> ,, <i>Alistipes</i> <i>massiliensis</i> , <i>Alistipes megaguti</i> , <i>Alistipes obesi</i> ,

				<i>Alistipes onderdonkii</i> , <i>Alistipes provencensis</i> , <i>Alistipes putredinis</i> , <i>Alistipes senegalensis</i> , , <i>Alistipes shahii</i> , <i>Alistipes timonensis</i>
<i>Betaproteobacteria</i>	<i>Burkholderiales</i>	<i>Alcaligenaceae</i>	<i>Paenkalcaligenes</i>	<i>Paenkalcaligenes hominis</i>
			<i>Bordella</i>	<i>Bordella pertussis</i>
		<i>Burkholderiaceae</i>	<i>Burkholderia</i>	<i>Burkholderia mallei</i> , <i>Burkholderia pseudomallei</i>
			<i>Ralstonia</i>	<i>Ralstonia solanacearum</i>
		<i>Neisseriaceae</i>	<i>Neisseria</i>	<i>Neisseria meningitidis</i>
		<i>Sutterellaceae</i>	<i>Sutterella</i>	<i>Sutterella parvirubra</i> , <i>Sutterella stercoricanis</i> , <i>Sutterella wadsworthensis</i>
<i>Clostridia</i>	<i>Clostridiales</i>	<i>Catabacteriaceae</i>	<i>Catabacter</i>	<i>Catabacter hongkongensis</i>
		<i>Clostridiaceae</i>	<i>Aminiphila</i>	<i>Anaerospaera aminiphila</i>
			<i>Christensenellaceae</i>	<i>C. massiliensis</i> , <i>C. minuta</i> , <i>C. timonensis</i>
			<i>Hungatella</i>	<i>Hungatella effluvia</i>
		<i>Eubacteriaceae</i>	<i>Eubacterium</i>	<i>Eubacterium contortum</i> , <i>Enterococcus durans</i> , <i>Eubacterium eligens</i> , <i>Eubacterium faecium</i> <i>Enterococcus faecalis</i> , <i>Enterococcus gallinarum</i> , <i>Eubacterium hadrum</i> , <i>Eubacterium hallii</i> , <i>Eubacterium limosum</i> , <i>Eubacterium ramulus</i> , <i>Eubacterium rectale</i> ,

				<i>Enterococcus villorum</i>
		<i>Lachnospiraceae</i>	<i>Anaerostipes</i>	<i>Anaerostipes caccae</i> , <i>Anaerostipes hadrus</i>
			<i>Blautia</i>	<i>Blautia hydrogenotrophica</i> , <i>Blautia massiliensis</i> , <i>Blautia stercoris</i> , <i>Blautia wexlerae</i>
			<i>Catonella</i>	<i>Catonella morbi</i>
			<i>Coprococcus</i>	<i>Coprococcus catus</i> , <i>Coprococcus comes</i> , <i>Coprococcus eutactus</i>
			<i>Dialister</i>	<i>Dialister invisus</i> , <i>Dialister micraeophilus</i> , <i>Dialister succinatiphilus</i>
			<i>Dorea</i>	<i>Dorea formicigenerans</i> , <i>Dorea longicatena</i> ,
			<i>Johnsonella</i>	<i>Johnsonella ignava</i>
			<i>Oribacterium</i>	<i>Oribacterium parvum</i> , <i>Oribacterium sinus</i>
			<i>Lachnobacterium</i>	
			<i>Lachnoclostridium</i>	
			<i>Lacrimispora</i>	<i>Lacrimispora sacchaarolytica</i>
			<i>Roseburia</i>	<i>Roseburia hominis</i> , <i>seburia intestinalis</i>
			<i>Tyzzereella</i>	<i>Tyzzereella nexilis</i>
		<i>Oscillospiraceae</i>	<i>Oscillibacter</i>	<i>Oscillibacter valericigenes</i>
			<i>Harryflintia</i>	<i>Harryflintia acetispora</i>
		<i>Peptococcaceae</i>		
		<i>Peptostreptococcaceae</i>	<i>Paraclostridium</i>	<i>Paraclostridium benzoelyticum</i>
			<i>Peptostreptococcus</i>	<i>Peptostreptococcus russellii</i>
		<i>Ruminococcaceae</i>		<i>Agathobaculum sp.</i>
			<i>Fournierella</i>	<i>Fournierella massiliensis</i>
			<i>Ruminococcus</i>	<i>Ruminococcus albus</i> , <i>Ruminococcus bromii</i> , <i>Ruminococcus callidus</i> , <i>Ruminococcus gnavus</i> , <i>Ruminococcus inulinivorans</i> ,

				<i>Ruminococcus obeum</i> , <i>Ruminococcus torques</i>
			<i>Faecalibacterium</i>	<i>Faecalibacterium prausnitzii</i>
		<i>Clostridiales family XIII/ Incertae sedis</i>		<i>Intestimonas butyriciproducens</i>
<i>Fusobacteria</i>	<i>Fusobacteriales</i>	<i>Fusobacteriaceae</i>	<i>Fusobacterium</i>	<i>Fusobacterium nucleatum</i> , <i>Fusobacterium naviforme</i>
		<i>Leptotrichiaceae</i>	<i>Leptotrichia</i>	
			<i>Sneathia</i>	
<i>Gammaproteobacteria</i>	<i>Enterobacterales</i>	<i>Enterobacteriaceae</i>	<i>Klebsiella</i>	<i>Klebsiella oxytoca</i> , <i>Klebsiella pneumoniae</i> , <i>Klebsiella quasipneumoniae</i> subsp. <i>Similipneumoniae</i> ,
			<i>Escherichia</i>	<i>Escherichia coli</i> strain Nissle 1917 (EcN) <i>Escherichia coli</i> strain ECOR12 <i>Escherichia coli</i> strain ECOR63
			<i>Shigella</i>	
<i>Negativicutes</i>		<i>Acidaminococcaceae</i>	<i>Acidaminococcus</i>	<i>Acidaminococcus fermentans</i> , <i>Acidaminococcus intestine</i>
			<i>Phascolarctobacterium</i>	<i>Phascolarctobacterium faecium</i> , <i>Phascolarctobacterium succinatutens</i>
		<i>Selenomonadaceae</i>	<i>Selenomonas</i>	<i>Selenomonas felix</i> , <i>Selenomonadales incertae sedis</i> , <i>Selenomonas sputigena</i>
		<i>Sporomusaceae</i>	<i>Selenomonadales</i>	
		<i>Veillonellaceae</i>	<i>Allisonella</i>	
			<i>Anaeroglobus</i>	<i>Anaeroglobus germinatus</i>
			<i>Caecibacter</i>	
			<i>Colibacter</i>	
			<i>Veillonella</i>	<i>Veillonella parvula</i>
			<i>Megasphaera</i>	<i>Megasphaera elsdenii</i> ,

				<i>Megasphaera massiliensis</i> , <i>Megasphaera micronuciformis</i> <i>Megasphaera sp</i>
			<i>Massilibacillus</i>	<i>Massilibacillus massiliensis</i>
			<i>Propionispira</i>	
			<i>Negativicoccus</i>	<i>Negativicoccus succinivornas</i>
			<i>Veillonella</i>	<i>Veillonella dispar</i> , <i>Veillonella parvula</i> , <i>Veillonella ratti</i> , <i>Veillonella tobetsuensis</i>
	<i>Synergistales</i>	<i>Synergistaceae</i>	<i>Aminobacterium</i>	<i>Aminobacterium mobile</i>
			<i>Cloacibacillus</i>	<i>Cloacibacillus evryensis</i>
			<i>Rarimicrobium</i>	<i>Rarimicrobium hominis</i>
<i>Verrucomicrobia</i>	<i>Verrucomicrobiales</i>	<i>Akkermansiaceae</i>	<i>Akkermansia</i>	<i>Akkermansia mucinophila</i>

Table 2: Exemplary Bacterial Strains

OTU	Public DB Accession
<i>Actinobacillus actinomycetemcomitans</i>	AY362885
<i>Actinobacillus minor</i>	ACFT01000025
<i>Actinobacillus pleuropneumoniae</i>	NR_074857
<i>Actinobacillus succinogenes</i>	CP000746
<i>Actinobacillus ureae</i>	AEVG01000167
<i>Actinobaculum massiliae</i>	AF487679
<i>Actinobaculum schaalii</i>	AY957507
<i>Actinobaculum sp. BM#101342</i>	AY282578
<i>Actinobaculum sp. P2P_19 P1</i>	AY207066
<i>Akkermansia muciniphila</i>	CP001071
<i>Alistipes finegoldii</i>	NR_043064
<i>Alistipes indistinctus</i>	AB490804
<i>Alistipes onderdonkii</i>	NR_043318
<i>Alistipes putredinis</i>	ABFK02000017
<i>Alistipes shahii</i>	FP929032
<i>Alistipes sp. HGB5</i>	AENZ01000082
<i>Alistipes sp. JC50</i>	JF824804
<i>Alistipes sp. RMA 9912</i>	GQ140629
<i>Anaerostipes caccae</i>	ABAX03000023
<i>Anaerostipes sp. 3_2_56FAA</i>	ACWB01000002
<i>Bacillus aeolius</i>	NR_025557
<i>Bacillus aerophilus</i>	NR_042339
<i>Bacillus aestuarii</i>	GQ980243
<i>Bacillus alcalophilus</i>	X76436
<i>Bacillus amyloliquefaciens</i>	NR_075005
<i>Bacillus anthracis</i>	AAEN01000020
<i>Bacillus atrophaeus</i>	NR_075016
<i>Bacillus badius</i>	NR_036893
<i>Bacillus cereus</i>	ABDJ01000015
<i>Bacillus circulans</i>	AB271747
<i>Bacillus clausii</i>	FN397477
<i>Bacillus coagulans</i>	DQ297928
<i>Bacillus firmus</i>	NR_025842
<i>Bacillus flexus</i>	NR_024691
<i>Bacillus fordii</i>	NR_025786
<i>Bacillus gelatini</i>	NR_025595
<i>Bacillus halmapalus</i>	NR_026144
<i>Bacillus halodurans</i>	AY144582
<i>Bacillus herbersteinensis</i>	NR_042286
<i>Bacillus horti</i>	NR_036860
<i>Bacillus idriensis</i>	NR_043268

<i>Bacillus lentus</i>	NR_040792
<i>Bacillus licheniformis</i>	NC_006270
<i>Bacillus megaterium</i>	GU252124
<i>Bacillus nealsonii</i>	NR_044546
<i>Bacillus niabensis</i>	NR_043334
<i>Bacillus niacini</i>	NR_024695
<i>Bacillus pocheonensis</i>	NR_041377
<i>Bacillus pumilus</i>	NR_074977
<i>Bacillus safensis</i>	JQ624766
<i>Bacillus simplex</i>	NR_042136
<i>Bacillus sonorensis</i>	NR_025130
<i>Bacillus sp. 10403023 MM10403188</i>	CAET01000089
<i>Bacillus sp. 2_A_57_CT2</i>	ACWD01000095
<i>Bacillus sp. 2008724126</i>	GU252108
<i>Bacillus sp. 2008724139</i>	GU252111
<i>Bacillus sp. 7_16AIA</i>	FN397518
<i>Bacillus sp. 9_3AIA</i>	FN397519
<i>Bacillus sp. AP8</i>	JX101689
<i>Bacillus sp. B27(2008)</i>	EU362173
<i>Bacillus sp. BT1B_CT2</i>	ACWC01000034
<i>Bacillus sp. GB1.1</i>	FJ897765
<i>Bacillus sp. GB9</i>	FJ897766
<i>Bacillus sp. HU19.1</i>	FJ897769
<i>Bacillus sp. HU29</i>	FJ897771
<i>Bacillus sp. HU33.1</i>	FJ897772
<i>Bacillus sp. JC6</i>	JF824800
<i>Bacillus sp. oral taxon F26</i>	HM099642
<i>Bacillus sp. oral taxon F28</i>	HM099650
<i>Bacillus sp. oral taxon F79</i>	HM099654
<i>Bacillus sp. SRC_DSF1</i>	GU797283
<i>Bacillus sp. SRC_DSF10</i>	GU797292
<i>Bacillus sp. SRC_DSF2</i>	GU797284
<i>Bacillus sp. SRC_DSF6</i>	GU797288
<i>Bacillus sp. tc09</i>	HQ844242
<i>Bacillus sp. zh168</i>	FJ851424
<i>Bacillus sphaericus</i>	DQ286318
<i>Bacillus sporothermodurans</i>	NR_026010
<i>Bacillus subtilis</i>	EU627588
<i>Bacillus thermoamylovorans</i>	NR_029151
<i>Bacillus weihenstephanensis</i>	NR_074926
<i>Bacteroidales bacterium ph8</i>	JN837494
<i>Bacteroidales genomosp. P1</i>	AY341819
<i>Bacteroidales genomosp. P2 oral clone MBI_G13</i>	DQ003613

<i>Bacteroidales genomsp. P3 oral clone MB1_G34</i>	DQ003615
<i>Bacteroidales genomsp. P4 oral clone MB2_G17</i>	DQ003617
<i>Bacteroidales genomsp. P5 oral clone MB2_P04</i>	DQ003619
<i>Bacteroidales genomsp. P6 oral clone MB3_C19</i>	DQ003634
<i>Bacteroidales genomsp. P7 oral clone MB3_P19</i>	DQ003623
<i>Bacteroidales genomsp. P8 oral clone MB4_G15</i>	DQ003626
<i>Bacteroides acidifaciens</i>	NR_028607
<i>Bacteroides barnesiæ</i>	NR_041446
<i>Bacteroides caccae</i>	EU136686
<i>Bacteroides cellulosilyticus</i>	ACCH01000108
<i>Bacteroides clarus</i>	AFBM01000011
<i>Bacteroides coagulans</i>	AB547639
<i>Bacteroides coprocola</i>	ABIY02000050
<i>Bacteroides coprophilus</i>	ACBW01000012
<i>Bacteroides dorei</i>	ABWZ01000093
<i>Bacteroides eggerthii</i>	ACWG01000065
<i>Bacteroides faecis</i>	GQ496624
<i>Bacteroides fingoldii</i>	AB222699
<i>Bacteroides fluxus</i>	AFBN01000029
<i>Bacteroides fragilis</i>	AP006841
<i>Bacteroides galacturonicus</i>	DQ497994
<i>Bacteroides helcogenes</i>	CP002352
<i>Bacteroides heparinolyticus</i>	JN867284
<i>Bacteroides intestinalis</i>	ABJL02000006
<i>Bacteroides massiliensis</i>	AB200226
<i>Bacteroides nordii</i>	NR_043017
<i>Bacteroides oleiciplenus</i>	AB547644
<i>Bacteroides ovatus</i>	ACWH01000036
<i>Bacteroides pectinophilus</i>	ABVQ01000036
<i>Bacteroides plebeius</i>	AB200218
<i>Bacteroides pyogenes</i>	NR_041280
<i>Bacteroides salanitronis</i>	CP002530
<i>Bacteroides salyersiae</i>	EU136690
<i>Bacteroides sp. 1_1_14</i>	ACRP01000155
<i>Bacteroides sp. 1_1_30</i>	ADCL01000128
<i>Bacteroides sp. 1_1_6</i>	ACIC01000215
<i>Bacteroides sp. 2_1_22</i>	ACPQ01000117
<i>Bacteroides sp. 2_1_56FAA</i>	ACWI01000065
<i>Bacteroides sp. 2_2_4</i>	ABZZ01000168
<i>Bacteroides sp. 20_3</i>	ACRQ01000064
<i>Bacteroides sp. 3_1_19</i>	ADCJ01000062
<i>Bacteroides sp. 3_1_23</i>	ACRS01000081
<i>Bacteroides sp. 3_1_33FAA</i>	ACPS01000085

<i>Bacteroides</i> sp. 3_1_40A	ACRT01000136
<i>Bacteroides</i> sp. 3_2_5	ACIB01000079
<i>Bacteroides</i> sp. 315_5	FJ848547
<i>Bacteroides</i> sp. 31SF15	AJ583248
<i>Bacteroides</i> sp. 31SF18	AJ583249
<i>Bacteroides</i> sp. 35AE31	AJ583244
<i>Bacteroides</i> sp. 35AE37	AJ583245
<i>Bacteroides</i> sp. 35BE34	AJ583246
<i>Bacteroides</i> sp. 35BE35	AJ583247
<i>Bacteroides</i> sp. 4_1_36	ACTC01000133
<i>Bacteroides</i> sp. 4_3_47FAA	ACDR02000029
<i>Bacteroides</i> sp. 9_1_42FAA	ACAA01000096
<i>Bacteroides</i> sp. AR20	AF139524
<i>Bacteroides</i> sp. AR29	AF139525
<i>Bacteroides</i> sp. B2	EU722733
<i>Bacteroides</i> sp. D1	ACAB02000030
<i>Bacteroides</i> sp. D2	ACGA01000077
<i>Bacteroides</i> sp. D20	ACPT01000052
<i>Bacteroides</i> sp. D22	ADCK01000151
<i>Bacteroides</i> sp. F_4	AB470322
<i>Bacteroides</i> sp. NB_8	AB117565
<i>Bacteroides</i> sp. WH2	AY895180
<i>Bacteroides</i> sp. XB12B	AM230648
<i>Bacteroides</i> sp. XB44A	AM230649
<i>Bacteroides stercoris</i>	ABFZ02000022
<i>Bacteroides thetaiotaomicron</i>	NR_074277
<i>Bacteroides uniformis</i>	AB050110
<i>Bacteroides ureolyticus</i>	GQ167666
<i>Bacteroides vulgatus</i>	CP000139
<i>Bacteroides xylanisolvens</i>	ADKP01000087
<i>Bacteroidetes bacterium</i> oral taxon D27	HM099638
<i>Bacteroidetes bacterium</i> oral taxon F31	HM099643
<i>Bacteroidetes bacterium</i> oral taxon F44	HM099649
<i>Barnesiella intestinihominis</i>	AB370251
<i>Bifidobacteriaceae genomosp. C1</i>	AY278612
<i>Bifidobacterium adolescentis</i>	AAXD02000018
<i>Bifidobacterium angulatum</i>	ABYS02000004
<i>Bifidobacterium animalis</i>	CP001606
<i>Bifidobacterium bifidum</i>	ABQP01000027
<i>Bifidobacterium breve</i>	CP002743
<i>Bifidobacterium catenulatum</i>	ABXY01000019
<i>Bifidobacterium dentium</i>	CP001750
<i>Bifidobacterium gallicum</i>	ABXB03000004

<i>Bifidobacterium infantis</i>	AY151398
<i>Bifidobacterium kashiwanohense</i>	AB491757
<i>Bifidobacterium longum</i>	ABQQ01000041
<i>Bifidobacterium pseudocatenulatum</i>	ABXX02000002
<i>Bifidobacterium pseudolongum</i>	NR_043442
<i>Bifidobacterium scardovii</i>	AJ307005
<i>Bifidobacterium sp. HM2</i>	AB425276
<i>Bifidobacterium sp. HMLN12</i>	JF519685
<i>Bifidobacterium sp. M45</i>	HM626176
<i>Bifidobacterium sp. MSX5B</i>	HQ616382
<i>Bifidobacterium sp. TM_7</i>	AB218972
<i>Bifidobacterium thermophilum</i>	DQ340557
<i>Bifidobacterium urinalis</i>	AJ278695
<i>Blautia coccoides</i>	AB571656
<i>Blautia glucerasea</i>	AB588023
<i>Blautia glucerasei</i>	AB439724
<i>Blautia hansenii</i>	ABYU02000037
<i>Blautia hydrogenotrophica</i>	ACBZ01000217
<i>Blautia luti</i>	AB691576
<i>Blautia producta</i>	AB600998
<i>Blautia schinkii</i>	NR_026312
<i>Blautia sp. M25</i>	HM626178
<i>Blautia stercoris</i>	HM626177
<i>Blautia wexlerae</i>	EF036467
<i>Bordetella bronchiseptica</i>	NR_025949
<i>Bordetella holmesii</i>	AB683187
<i>Bordetella parapertussis</i>	NR_025950
<i>Bordetella pertussis</i>	BX640418
<i>Borrelia afzelii</i>	ABCU01000001
<i>Borrelia burgdorferi</i>	ABGI01000001
<i>Borrelia crocidurae</i>	DQ057990
<i>Borrelia duttonii</i>	NC_011229
<i>Borrelia garinii</i>	ABJV01000001
<i>Borrelia hermsii</i>	AY597657
<i>Borrelia hispanica</i>	DQ057988
<i>Borrelia persica</i>	HM161645
<i>Borrelia recurrentis</i>	AF107367
<i>Borrelia sp. NE49</i>	AJ224142
<i>Borrelia spielmanii</i>	ABKB01000002
<i>Borrelia turicatae</i>	NC_008710
<i>Borrelia valaisiana</i>	ABCY01000002
<i>Brucella ovis</i>	NC_009504
<i>Brucella sp. 83_13</i>	ACBQ01000040

<i>Brucella</i> sp. BO1	EU053207
<i>Brucella suis</i>	ACBK01000034
<i>Burkholderia ambifaria</i>	AAUZ01000009
<i>Burkholderia cenocepacia</i>	AAHI01000060
<i>Burkholderia cepacia</i>	NR_041719
<i>Burkholderia mallei</i>	CP000547
<i>Burkholderia multivorans</i>	NC_010086
<i>Burkholderia oklahomensis</i>	DQ108388
<i>Burkholderia pseudomallei</i>	CP001408
<i>Burkholderia rhizoxinica</i>	HQ005410
<i>Burkholderia</i> sp. 383	CP000151
<i>Burkholderia xenovorans</i>	U86373
<i>Burkholderiales</i> bacterium 1_1_47	ADCQ01000066
<i>Butyrivibrio crossotus</i>	ABWN01000012
<i>Butyrivibrio fibrisolvens</i>	U41172
<i>Chlamydia muridarum</i>	AE002160
<i>Chlamydia psittaci</i>	NR_036864
<i>Chlamydia trachomatis</i>	U68443
<i>Chlamydiales</i> bacterium NS11	JN606074
<i>Citrobacter amalonaticus</i>	FR870441
<i>Citrobacter braakii</i>	NR_028687
<i>Citrobacter farmeri</i>	AF025371
<i>Citrobacter freundii</i>	NR_028894
<i>Citrobacter gillenii</i>	AF025367
<i>Citrobacter koseri</i>	NC_009792
<i>Citrobacter murlinae</i>	AF025369
<i>Citrobacter rodentium</i>	NR_074903
<i>Citrobacter sedlakii</i>	AF025364
<i>Citrobacter</i> sp. 30_2	ACDJ01000053
<i>Citrobacter</i> sp. KMSI_3	GQ468398
<i>Citrobacter werkmanii</i>	AF025373
<i>Citrobacter youngae</i>	ABWL02000011
<i>Cloacibacillus evryensis</i>	GQ258966
<i>Clostridiaceae</i> bacterium END_2	EF451053
<i>Clostridiaceae</i> bacterium JC13	JF824807
<i>Clostridiales</i> bacterium 1_7_47FAA	ABQR01000074
<i>Clostridiales</i> bacterium 9400853	HM587320
<i>Clostridiales</i> bacterium 9403326	HM587324
<i>Clostridiales</i> bacterium oral clone P4PA_66 P1	AY207065
<i>Clostridiales</i> bacterium oral taxon 093	GQ422712
<i>Clostridiales</i> bacterium oral taxon F32	HM099644
<i>Clostridiales</i> bacterium ph2	JN837487
<i>Clostridiales</i> bacterium SY8519	AB477431

<i>Clostridiales</i> genomsp. BVAB3	CP001850
<i>Clostridiales</i> sp. SM4_1	FP929060
<i>Clostridiales</i> sp. SS3_4	AY305316
<i>Clostridiales</i> sp. SSC_2	FP929061
<i>Clostridium acetobutylicum</i>	NR_074511
<i>Clostridium aerotolerans</i>	X76163
<i>Clostridium aldenense</i>	NR_043680
<i>Clostridium aldrichii</i>	NR_026099
<i>Clostridium algidicarnis</i>	NR_041746
<i>Clostridium algidixylanolyticum</i>	NR_028726
<i>Clostridium aminovalericum</i>	NR_029245
<i>Clostridium amygdalinum</i>	AY353957
<i>Clostridium argentinense</i>	NR_029232
<i>Clostridium asparagiforme</i>	ACCJ01000522
<i>Clostridium baratii</i>	NR_029229
<i>Clostridium bartlettii</i>	ABEZ02000012
<i>Clostridium beijerinckii</i>	NR_074434
<i>Clostridium bifermentans</i>	X73437
<i>Clostridium bolteae</i>	ABCC02000039
<i>Clostridium botulinum</i>	NC_010723
<i>Clostridium butyricum</i>	ABDT01000017
<i>Clostridium cadaveris</i>	AB542932
<i>Clostridium carboxidivorans</i>	FR733710
<i>Clostridium carnis</i>	NR_044716
<i>Clostridium celatum</i>	X77844
<i>Clostridium celerecrescens</i>	JQ246092
<i>Clostridium cellulosi</i>	NR_044624
<i>Clostridium chauvoei</i>	EU106372
<i>Clostridium citroniae</i>	ADLJ01000059
<i>Clostridium clariflavum</i>	NR_041235
<i>Clostridium clostridiiformes</i>	M59089
<i>Clostridium clostridioforme</i>	NR_044715
<i>Clostridium coccoides</i>	EF025906
<i>Clostridium cochlearium</i>	NR_044717
<i>Clostridium cocleatum</i>	NR_026495
<i>Clostridium colicanis</i>	FJ957863
<i>Clostridium colinum</i>	NR_026151
<i>Clostridium difficile</i>	NC_013315
<i>Clostridium disporicum</i>	NR_026491
<i>Clostridium estertheticum</i>	NR_042153
<i>Clostridium fallax</i>	NR_044714
<i>Clostridium favosporum</i>	X76749
<i>Clostridium felsineum</i>	AF270502

<i>Clostridium frigidicarnis</i>	NR_024919
<i>Clostridium gasigenes</i>	NR_024945
<i>Clostridium ghonii</i>	AB542933
<i>Clostridium glycolicum</i>	FJ384385
<i>Clostridium glycyrrhizinilyticum</i>	AB233029
<i>Clostridium haemolyticum</i>	NR_024749
<i>Clostridium hathewayi</i>	AY552788
<i>Clostridium hiranonis</i>	AB023970
<i>Clostridium histolyticum</i>	HF558362
<i>Clostridium hylemonae</i>	AB023973
<i>Clostridium indolis</i>	AF028351
<i>Clostridium innocuum</i>	M23732
<i>Clostridium irregulare</i>	NR_029249
<i>Clostridium isatidis</i>	NR_026347
<i>Clostridium kluyveri</i>	NR_074165
<i>Clostridium lactatifermentans</i>	NR_025651
<i>Clostridium lavalense</i>	EF564277
<i>Clostridium leptum</i>	AJ305238
<i>Clostridium limosum</i>	FR870444
<i>Clostridium magnum</i>	X77835
<i>Clostridium malenominatum</i>	FR749893
<i>Clostridium mayombeii</i>	FR733682
<i>Clostridium methylpentosum</i>	ACEC01000059
<i>Clostridium nexile</i>	X73443
<i>Clostridium novyi</i>	NR_074343
<i>Clostridium orbiscindens</i>	Y18187
<i>Clostridium oroticum</i>	FR749922
<i>Clostridium paraputrificum</i>	AB536771
<i>Clostridium perfringens</i>	ABDW01000023
<i>Clostridium phytofermentans</i>	NR_074652
<i>Clostridium piliforme</i>	D14639
<i>Clostridium putrefaciens</i>	NR_024995
<i>Clostridium quinii</i>	NR_026149
<i>Clostridium ramosum</i>	M23731
<i>Clostridium rectum</i>	NR_029271
<i>Clostridium saccharogumia</i>	DQ100445
<i>Clostridium saccharolyticum</i>	CP002109
<i>Clostridium sardiniense</i>	NR_041006
<i>Clostridium sartagoforme</i>	NR_026490
<i>Clostridium scindens</i>	AF262238
<i>Clostridium septicum</i>	NR_026020
<i>Clostridium sordellii</i>	AB448946
<i>Clostridium</i> sp. 7_2_43FAA	ACDK01000101

<i>Clostridium</i> sp. D5	ADBG01000142
<i>Clostridium</i> sp. HGF2	AENW01000022
<i>Clostridium</i> sp. HPB_46	AY862516
<i>Clostridium</i> sp. JC122	CAEV01000127
<i>Clostridium</i> sp. L2_50	AAYW02000018
<i>Clostridium</i> sp. LMG 16094	X95274
<i>Clostridium</i> sp. M62_1	ACFX02000046
<i>Clostridium</i> sp. MLG055	AF304435
<i>Clostridium</i> sp. MT4 E	FJ159523
<i>Clostridium</i> sp. NMBHI_1	JN093130
<i>Clostridium</i> sp. NML 04A032	EU815224
<i>Clostridium</i> sp. SS2_1	ABGC03000041
<i>Clostridium</i> sp. SY8519	AP012212
<i>Clostridium</i> sp. TM_40	AB249652
<i>Clostridium</i> sp. YIT 12069	AB491207
<i>Clostridium</i> sp. YIT 12070	AB491208
<i>Clostridium sphenoides</i>	X73449
<i>Clostridium spiroforme</i>	X73441
<i>Clostridium sporogenes</i>	ABKW02000003
<i>Clostridium sporosphaeroides</i>	NR_044835
<i>Clostridium stercorarium</i>	NR_025100
<i>Clostridium sticklandii</i>	L04167
<i>Clostridium straminisolvens</i>	NR_024829
<i>Clostridium subterminale</i>	NR_041795
<i>Clostridium sulfidigenes</i>	NR_044161
<i>Clostridium symbiosum</i>	ADLQ01000114
<i>Clostridium tertium</i>	Y18174
<i>Clostridium tetani</i>	NC_004557
<i>Clostridium thermocellum</i>	NR_074629
<i>Clostridium tyrobutyricum</i>	NR_044718
<i>Clostridium viride</i>	NR_026204
<i>Clostridium xylanolyticum</i>	NR_037068
<i>Collinsella aerofaciens</i>	AAVN02000007
<i>Collinsella intestinalis</i>	ABXH02000037
<i>Collinsella stercoris</i>	ABXJ01000150
<i>Collinsella tanakaei</i>	AB490807
<i>Coprobacillus cateniformis</i>	AB030218
<i>Coprobacillus</i> sp. 29_1	ADKX01000057
<i>Coprobacillus</i> sp. D7	ACDT01000199
<i>Coprococcus catus</i>	EU266552
<i>Coprococcus comes</i>	ABVR01000038
<i>Coprococcus eutactus</i>	EF031543
<i>Coprococcus</i> sp. ART55_1	AY350746

<i>Dialister invisus</i>	ACIM02000001
<i>Dialister microaerophilus</i>	AFBB01000028
<i>Dialister microaerophilus</i>	AENT01000008
<i>Dialister pneumosintes</i>	HM596297
<i>Dialister propionificiens</i>	NR_043231
<i>Dialister sp. oral taxon 502</i>	GQ422739
<i>Dialister succinatiphilus</i>	AB370249
<i>Dorea formicigenerans</i>	AAXA02000006
<i>Dorea longicatena</i>	AJ132842
<i>Enhydrobacter aerosaccus</i>	ACYI01000081
<i>Enterobacter aerogenes</i>	AJ251468
<i>Enterobacter asburiae</i>	NR_024640
<i>Enterobacter cancerogenus</i>	Z96078
<i>Enterobacter cloacae</i>	FP929040
<i>Enterobacter cowanii</i>	NR_025566
<i>Enterobacter hormaechei</i>	AFHR01000079
<i>Enterobacter sp. 247BMC</i>	HQ122932
<i>Enterobacter sp. 638</i>	NR_074777
<i>Enterobacter sp. JC163</i>	JN657217
<i>Enterobacter sp. SCSS</i>	HM007811
<i>Enterobacter sp. TSE38</i>	HM156134
<i>Enterobacteriaceae bacterium 9_2_54FAA</i>	ADCU01000033
<i>Enterobacteriaceae bacterium CF01Ent_1</i>	AJ489826
<i>Enterobacteriaceae bacterium Smarlab 3302238</i>	AY538694
<i>Enterococcus avium</i>	AF133535
<i>Enterococcus caccae</i>	AY943820
<i>Enterococcus casseliflavus</i>	AEWT01000047
<i>Enterococcus durans</i>	AJ276354
<i>Enterococcus faecalis</i>	AE016830
<i>Enterococcus faecium</i>	AM157434
<i>Enterococcus gallinarum</i>	AB269767
<i>Enterococcus gilvus</i>	AY033814
<i>Enterococcus hawaiiensis</i>	AY321377
<i>Enterococcus hirae</i>	AF061011
<i>Enterococcus italicus</i>	AEPV01000109
<i>Enterococcus mundtii</i>	NR_024906
<i>Enterococcus raffinosus</i>	FN600541
<i>Enterococcus sp. BV2CASA2</i>	JN809766
<i>Enterococcus sp. CCRI_16620</i>	GU457263
<i>Enterococcus sp. F95</i>	FJ463817
<i>Enterococcus sp. RfL6</i>	AJ133478
<i>Enterococcus thailandicus</i>	AY321376
<i>Erysipelotrichaceae bacterium 3_1_53</i>	ACTJ01000113

<i>Erysipelotrichaceae bacterium 5_2_54FAA</i>	ACZW01000054
<i>Escherichia albertii</i>	ABKX01000012
<i>Escherichia coli</i>	NC_008563
<i>Escherichia fergusonii</i>	CU928158
<i>Escherichia hermannii</i>	HQ407266
<i>Escherichia sp. 1_1_43</i>	ACID01000033
<i>Escherichia sp. 4_1_40B</i>	ACDM02000056
<i>Escherichia sp. B4</i>	EU722735
<i>Escherichia vulneris</i>	NR_041927
<i>Eubacteriaceae bacterium P4P_50 P4</i>	AY207060
<i>Eubacterium barkeri</i>	NR_044661
<i>Eubacterium bifforme</i>	ABYT01000002
<i>Eubacterium brachy</i>	U13038
<i>Eubacterium budayi</i>	NR_024682
<i>Eubacterium callanderi</i>	NR_026330
<i>Eubacterium cellulosolvens</i>	AY178842
<i>Eubacterium contortum</i>	FR749946
<i>Eubacterium coprostanoligenes</i>	HM037995
<i>Eubacterium cylindroides</i>	FP929041
<i>Eubacterium desmolans</i>	NR_044644
<i>Eubacterium dolichum</i>	L34682
<i>Eubacterium eligens</i>	CP001104
<i>Eubacterium fissicatena</i>	FR749935
<i>Eubacterium hadrum</i>	FR749933
<i>Eubacterium hallii</i>	L34621
<i>Eubacterium infirmum</i>	U13039
<i>Eubacterium limosum</i>	CP002273
<i>Eubacterium moniliforme</i>	HF558373
<i>Eubacterium multiforme</i>	NR_024683
<i>Eubacterium nitritogenes</i>	NR_024684
<i>Eubacterium nodatum</i>	U13041
<i>Eubacterium ramulus</i>	AJ011522
<i>Eubacterium rectale</i>	FP929042
<i>Eubacterium ruminantium</i>	NR_024661
<i>Eubacterium saburreum</i>	AB525414
<i>Eubacterium saphenum</i>	NR_026031
<i>Eubacterium siraeum</i>	ABCA03000054
<i>Eubacterium sp. 3_1_31</i>	ACTL01000045
<i>Eubacterium sp. AS15b</i>	HQ616364
<i>Eubacterium sp. OBRC9</i>	HQ616354
<i>Eubacterium sp. oral clone GI038</i>	AY349374
<i>Eubacterium sp. oral clone IR009</i>	AY349376
<i>Eubacterium sp. oral clone JH012</i>	AY349373

<i>Eubacterium</i> sp. oral clone JI012	AY349379
<i>Eubacterium</i> sp. oral clone JN088	AY349377
<i>Eubacterium</i> sp. oral clone JS001	AY349378
<i>Eubacterium</i> sp. oral clone OH3A	AY947497
<i>Eubacterium</i> sp. WAL 14571	FJ687606
<i>Eubacterium tenue</i>	M59118
<i>Eubacterium tortuosum</i>	NR_044648
<i>Eubacterium ventriosum</i>	L34421
<i>Eubacterium xylanophilum</i>	L34628
<i>Eubacterium yurii</i>	AEES01000073
<i>Fusobacterium canifelinum</i>	AY162222
<i>Fusobacterium genomosp. C1</i>	AY278616
<i>Fusobacterium genomosp. C2</i>	AY278617
<i>Fusobacterium gonidiaformans</i>	ACET01000043
<i>Fusobacterium mortiferum</i>	ACDB02000034
<i>Fusobacterium naviforme</i>	HQ223106
<i>Fusobacterium necrogenes</i>	X55408
<i>Fusobacterium necrophorum</i>	AM905356
<i>Fusobacterium nucleatum</i>	ADV01000034
<i>Fusobacterium periodonticum</i>	ACJY01000002
<i>Fusobacterium russii</i>	NR_044687
<i>Fusobacterium</i> sp. 1_1_41FAA	ADGG01000053
<i>Fusobacterium</i> sp. 11_3_2	ACUO01000052
<i>Fusobacterium</i> sp. 12_1B	AGWJ01000070
<i>Fusobacterium</i> sp. 2_1_31	ACDC02000018
<i>Fusobacterium</i> sp. 3_1_27	ADGF01000045
<i>Fusobacterium</i> sp. 3_1_33	ACQE01000178
<i>Fusobacterium</i> sp. 3_1_36A2	ACPU01000044
<i>Fusobacterium</i> sp. 3_1_5R	ACDD01000078
<i>Fusobacterium</i> sp. AC18	HQ616357
<i>Fusobacterium</i> sp. ACB2	HQ616358
<i>Fusobacterium</i> sp. AS2	HQ616361
<i>Fusobacterium</i> sp. CM1	HQ616371
<i>Fusobacterium</i> sp. CM21	HQ616375
<i>Fusobacterium</i> sp. CM22	HQ616376
<i>Fusobacterium</i> sp. D12	ACDG02000036
<i>Fusobacterium</i> sp. oral clone ASCF06	AY923141
<i>Fusobacterium</i> sp. oral clone ASCF11	AY953256
<i>Fusobacterium ulcerans</i>	ACDH01000090
<i>Fusobacterium varium</i>	ACIE01000009
<i>Gemella haemolysans</i>	ACDZ02000012
<i>Gemella morbillorum</i>	NR_025904
<i>Gemella morbillorum</i>	ACRX01000010

<i>Gemella sanguinis</i>	ACRY01000057
<i>Gemella</i> sp. oral clone ASCE02	AY923133
<i>Gemella</i> sp. oral clone ASCF04	AY923139
<i>Gemella</i> sp. oral clone ASCF12	AY923143
<i>Gemella</i> sp. WAL 1945J	EU427463
<i>Klebsiella oxytoca</i>	AY292871
<i>Klebsiella pneumoniae</i>	CP000647
<i>Klebsiella</i> sp. AS10	HQ616362
<i>Klebsiella</i> sp. Co9935	DQ068764
<i>Klebsiella</i> sp. enrichment culture clone SRC_DSD25	HM195210
<i>Klebsiella</i> sp. OBRC7	HQ616353
<i>Klebsiella</i> sp. SP_BA	FJ999767
<i>Klebsiella</i> sp. SRC_DSD1	GU797254
<i>Klebsiella</i> sp. SRC_DSD11	GU797263
<i>Klebsiella</i> sp. SRC_DSD12	GU797264
<i>Klebsiella</i> sp. SRC_DSD15	GU797267
<i>Klebsiella</i> sp. SRC_DSD2	GU797253
<i>Klebsiella</i> sp. SRC_DSD6	GU797258
<i>Klebsiella variicola</i>	CP001891
<i>Lachnobacterium bovis</i>	GU324407
<i>Lachnospira multipara</i>	FR733699
<i>Lachnospira pectinoschiza</i>	L14675
<i>Lachnospiraceae</i> bacterium 1_1_57FAA	ACTM01000065
<i>Lachnospiraceae</i> bacterium 1_4_56FAA	ACTN01000028
<i>Lachnospiraceae</i> bacterium 2_1_46FAA	ADLB01000035
<i>Lachnospiraceae</i> bacterium 2_1_58FAA	ACTO01000052
<i>Lachnospiraceae</i> bacterium 3_1_57FAA_CT1	ACTP01000124
<i>Lachnospiraceae</i> bacterium 4_1_37FAA	ADCR01000030
<i>Lachnospiraceae</i> bacterium 5_1_57FAA	ACTR01000020
<i>Lachnospiraceae</i> bacterium 5_1_63FAA	ACTS01000081
<i>Lachnospiraceae</i> bacterium 6_1_63FAA	ACTV01000014
<i>Lachnospiraceae</i> bacterium 8_1_57FAA	ACWQ01000079
<i>Lachnospiraceae</i> bacterium 9_1_43BFAA	ACTX01000023
<i>Lachnospiraceae</i> bacterium A4	DQ789118
<i>Lachnospiraceae</i> bacterium DJF VP30	EU728771
<i>Lachnospiraceae</i> bacterium ICM62	HQ616401
<i>Lachnospiraceae</i> bacterium MSX33	HQ616384
<i>Lachnospiraceae</i> bacterium oral taxon 107	ADDS01000069
<i>Lachnospiraceae</i> bacterium oral taxon F15	HM099641
<i>Lachnospiraceae</i> genomosp. C1	AY278618
<i>Lactobacillus acidipiscis</i>	NR_024718
<i>Lactobacillus acidophilus</i>	CP000033
<i>Lactobacillus alimentarius</i>	NR_044701

<i>Lactobacillus amylolyticus</i>	ADNY01000006
<i>Lactobacillus amylovorus</i>	CP002338
<i>Lactobacillus antri</i>	ACLL01000037
<i>Lactobacillus brevis</i>	EU194349
<i>Lactobacillus buchneri</i>	ACGH01000101
<i>Lactobacillus casei</i>	CP000423
<i>Lactobacillus catenaformis</i>	M23729
<i>Lactobacillus coleohominis</i>	ACOH01000030
<i>Lactobacillus coryniformis</i>	NR_044705
<i>Lactobacillus crispatus</i>	ACOG01000151
<i>Lactobacillus curvatus</i>	NR_042437
<i>Lactobacillus delbrueckii</i>	CP002341
<i>Lactobacillus dextrinicus</i>	NR_036861
<i>Lactobacillus farciminis</i>	NR_044707
<i>Lactobacillus fermentum</i>	CP002033
<i>Lactobacillus gasseri</i>	ACOZ01000018
<i>Lactobacillus gastricus</i>	AICN01000060
<i>Lactobacillus genomosp. C1</i>	AY278619
<i>Lactobacillus genomosp. C2</i>	AY278620
<i>Lactobacillus helveticus</i>	ACLM01000202
<i>Lactobacillus hilgardii</i>	ACGP01000200
<i>Lactobacillus hominis</i>	FR681902
<i>Lactobacillus iners</i>	AEKJ01000002
<i>Lactobacillus jensenii</i>	ACQD01000066
<i>Lactobacillus johnsonii</i>	AE017198
<i>Lactobacillus kalixensis</i>	NR_029083
<i>Lactobacillus kefiranoformis</i>	NR_042440
<i>Lactobacillus kefir</i>	NR_042230
<i>Lactobacillus kimchii</i>	NR_025045
<i>Lactobacillus leichmannii</i>	JX986966
<i>Lactobacillus mucosae</i>	FR693800
<i>Lactobacillus murinus</i>	NR_042231
<i>Lactobacillus nodensis</i>	NR_041629
<i>Lactobacillus oeni</i>	NR_043095
<i>Lactobacillus oris</i>	AEKL01000077
<i>Lactobacillus parabrevis</i>	NR_042456
<i>Lactobacillus parabuchneri</i>	NR_041294
<i>Lactobacillus paracasei</i>	ABQV01000067
<i>Lactobacillus parakefir</i>	NR_029039
<i>Lactobacillus pentosus</i>	JN813103
<i>Lactobacillus perolens</i>	NR_029360
<i>Lactobacillus plantarum</i>	ACGZ02000033
<i>Lactobacillus pontis</i>	HM218420

<i>Lactobacillus reuteri</i>	ACGW02000012
<i>Lactobacillus rhamnosus</i>	ABWJ01000068
<i>Lactobacillus rogosae</i>	GU269544
<i>Lactobacillus ruminis</i>	ACGS02000043
<i>Lactobacillus sakei</i>	DQ989236
<i>Lactobacillus salivarius</i>	AEBA01000145
<i>Lactobacillus saniviri</i>	AB602569
<i>Lactobacillus senioris</i>	AB602570
<i>Lactobacillus sp. 66c</i>	FR681900
<i>Lactobacillus sp. BT6</i>	HQ616370
<i>Lactobacillus sp. KLDS 1.0701</i>	EU600905
<i>Lactobacillus sp. KLDS 1.0702</i>	EU600906
<i>Lactobacillus sp. KLDS 1.0703</i>	EU600907
<i>Lactobacillus sp. KLDS 1.0704</i>	EU600908
<i>Lactobacillus sp. KLDS 1.0705</i>	EU600909
<i>Lactobacillus sp. KLDS 1.0707</i>	EU600911
<i>Lactobacillus sp. KLDS 1.0709</i>	EU600913
<i>Lactobacillus sp. KLDS 1.0711</i>	EU600915
<i>Lactobacillus sp. KLDS 1.0712</i>	EU600916
<i>Lactobacillus sp. KLDS 1.0713</i>	EU600917
<i>Lactobacillus sp. KLDS 1.0716</i>	EU600921
<i>Lactobacillus sp. KLDS 1.0718</i>	EU600922
<i>Lactobacillus sp. KLDS 1.0719</i>	EU600923
<i>Lactobacillus sp. oral clone HT002</i>	AY349382
<i>Lactobacillus sp. oral clone HT070</i>	AY349383
<i>Lactobacillus sp. oral taxon 052</i>	GQ422710
<i>Lactobacillus tucseti</i>	NR_042194
<i>Lactobacillus ultunensis</i>	ACGU01000081
<i>Lactobacillus vaginalis</i>	ACGV01000168
<i>Lactobacillus vini</i>	NR_042196
<i>Lactobacillus vitulinus</i>	NR_041305
<i>Lactobacillus zeae</i>	NR_037122
<i>Lactococcus garvieae</i>	AF061005
<i>Lactococcus lactis</i>	CP002365
<i>Lactococcus raffinolactis</i>	NR_044359
<i>Listeria grayi</i>	ACCR02000003
<i>Listeria innocua</i>	JF967625
<i>Listeria ivanovii</i>	X56151
<i>Listeria monocytogenes</i>	CP002003
<i>Listeria welshimeri</i>	AM263198
<i>Megasphaera elsdenii</i>	AY038996
<i>Megasphaera genomsp. C1</i>	AY278622
<i>Megasphaera genomsp. type_1</i>	ADGP01000010

<i>Megasphaera micronuciformis</i>	AECS01000020
<i>Megasphaera</i> sp. BLPYG_07	HM990964
<i>Megasphaera</i> sp. UPII 199_6	AFIJ01000040
<i>Microbacterium gubbeenense</i>	NR_025098
<i>Microbacterium lacticum</i>	EU714351
<i>Mitsuokella jalaludinii</i>	NR_028840
<i>Mitsuokella multacida</i>	ABWK02000005
<i>Mitsuokella</i> sp. oral taxon 521	GU413658
<i>Mitsuokella</i> sp. oral taxon G68	GU432166
<i>Mycobacterium abscessus</i>	AGQU01000002
<i>Mycobacterium africanum</i>	AF480605
<i>Mycobacterium alsiensis</i>	AJ938169
<i>Mycobacterium avium</i>	CP000479
<i>Mycobacterium chelonae</i>	AB548610
<i>Mycobacterium colombiense</i>	AM062764
<i>Mycobacterium elephantis</i>	AF385898
<i>Mycobacterium gordonae</i>	GU142930
<i>Mycobacterium intracellulare</i>	GQ153276
<i>Mycobacterium kansasii</i>	AF480601
<i>Mycobacterium lacus</i>	NR_025175
<i>Mycobacterium leprae</i>	FM211192
<i>Mycobacterium lepromatosis</i>	EU203590
<i>Mycobacterium mageritense</i>	FR798914
<i>Mycobacterium mantenii</i>	FJ042897
<i>Mycobacterium marinum</i>	NC_010612
<i>Mycobacterium microti</i>	NR_025234
<i>Mycobacterium neoaurum</i>	AF268445
<i>Mycobacterium parascrofulaceum</i>	ADNV01000350
<i>Mycobacterium paraterrae</i>	EU919229
<i>Mycobacterium phlei</i>	GU142920
<i>Mycobacterium seoulense</i>	DQ536403
<i>Mycobacterium smegmatis</i>	CP000480
<i>Mycobacterium</i> sp. 1761	EU703150
<i>Mycobacterium</i> sp. 1776	EU703152
<i>Mycobacterium</i> sp. 1781	EU703147
<i>Mycobacterium</i> sp. 1791	EU703148
<i>Mycobacterium</i> sp. 1797	EU703149
<i>Mycobacterium</i> sp. AQ1GA4	HM210417
<i>Mycobacterium</i> sp. B10_07.09.0206	HQ174245
<i>Mycobacterium</i> sp. GN_10546	FJ497243
<i>Mycobacterium</i> sp. GN_10827	FJ497247
<i>Mycobacterium</i> sp. GN_11124	FJ652846
<i>Mycobacterium</i> sp. GN_9188	FJ497240

<i>Mycobacterium</i> sp. GR_2007_210	FJ555538
<i>Mycobacterium</i> sp. HE5	AJ012738
<i>Mycobacterium</i> sp. NLA001000736	HM627011
<i>Mycobacterium</i> sp. W	DQ437715
<i>Mycobacterium tuberculosis</i>	CP001658
<i>Mycobacterium ulcerans</i>	AB548725
<i>Mycobacterium vulneris</i>	EU834055
<i>Mycoplasma agalactiae</i>	AF010477
<i>Mycoplasma amphoriforme</i>	AY531656
<i>Mycoplasma arthritidis</i>	NC_011025
<i>Mycoplasma bovoculi</i>	NR_025987
<i>Mycoplasma faucium</i>	NR_024983
<i>Mycoplasma fermentans</i>	CP002458
<i>Mycoplasma flocculare</i>	X62699
<i>Mycoplasma genitalium</i>	L43967
<i>Mycoplasma hominis</i>	AF443616
<i>Mycoplasma orale</i>	AY796060
<i>Mycoplasma ovipneumoniae</i>	NR_025989
<i>Mycoplasma penetrans</i>	NC_004432
<i>Mycoplasma pneumoniae</i>	NC_000912
<i>Mycoplasma putrefaciens</i>	U26055
<i>Mycoplasma salivarium</i>	M24661
<i>Mycoplasmataceae</i> genomsp. P1 oral clone MB1_G23	DQ003614
<i>Neisseria bacilliformis</i>	AFAY01000058
<i>Neisseria cinerea</i>	ACDY01000037
<i>Neisseria elongata</i>	ADBF01000003
<i>Neisseria flavescens</i>	ACQV01000025
<i>Neisseria</i> genomsp. P2 oral clone MB5_P15	DQ003630
<i>Neisseria gonorrhoeae</i>	CP002440
<i>Neisseria lactamica</i>	ACEQ01000095
<i>Neisseria macacae</i>	AFQE01000146
<i>Neisseria meningitidis</i>	NC_003112
<i>Neisseria mucosa</i>	ACDX01000110
<i>Neisseria pharyngis</i>	AJ239281
<i>Neisseria polysaccharea</i>	ADBE01000137
<i>Neisseria sicca</i>	ACKO02000016
<i>Neisseria</i> sp. KEM232	GQ203291
<i>Neisseria</i> sp. oral clone AP132	AY005027
<i>Neisseria</i> sp. oral clone JC012	AY349388
<i>Neisseria</i> sp. oral strain B33KA	AY005028
<i>Neisseria</i> sp. oral taxon 014	ADEA01000039
<i>Neisseria</i> sp. SMC_A9199	FJ763637
<i>Neisseria</i> sp. TM10_1	DQ279352

<i>Neisseria subflava</i>	ACEO01000067
<i>Odoribacter laneus</i>	AB490805
<i>Odoribacter splanchnicus</i>	CP002544
<i>Oscillibacter</i> sp. G2	HM626173
<i>Oscillibacter valericigenes</i>	NR_074793
<i>Oscillospira guilliermondii</i>	AB040495
<i>Paenibacillus barcinonensis</i>	NR_042272
<i>Paenibacillus barengoltzii</i>	NR_042756
<i>Paenibacillus chibensis</i>	NR_040885
<i>Paenibacillus cookii</i>	NR_025372
<i>Paenibacillus durus</i>	NR_037017
<i>Paenibacillus glucanolyticus</i>	D78470
<i>Paenibacillus lactis</i>	NR_025739
<i>Paenibacillus lautus</i>	NR_040882
<i>Paenibacillus pabuli</i>	NR_040853
<i>Paenibacillus polymyxa</i>	NR_037006
<i>Paenibacillus popilliae</i>	NR_040888
<i>Paenibacillus</i> sp. CIP 101062	HM212646
<i>Parabacteroides distasonis</i>	CP000140
<i>Parabacteroides goldsteinii</i>	AY974070
<i>Parabacteroides gordonii</i>	AB470344
<i>Parabacteroides johnsonii</i>	ABYH01000014
<i>Parabacteroides merdae</i>	EU136685
<i>Parabacteroides</i> sp. D13	ACPW01000017
<i>Parabacteroides</i> sp. NS31_3	JN029805
<i>Peptococcus niger</i>	NR_029221
<i>Peptococcus</i> sp. oral clone JM048	AY349389
<i>Peptococcus</i> sp. oral taxon 167	GQ422727
<i>Peptoniphilus asaccharolyticus</i>	D14145
<i>Peptoniphilus duerdenii</i>	EU526290
<i>Peptoniphilus harei</i>	NR_026358
<i>Peptoniphilus indolicus</i>	AY153431
<i>Peptoniphilus ivorii</i>	Y07840
<i>Peptoniphilus lacrimalis</i>	ADDO01000050
<i>Peptoniphilus</i> sp. gpac007	AM176517
<i>Peptoniphilus</i> sp. gpac018A	AM176519
<i>Peptoniphilus</i> sp. gpac077	AM176527
<i>Peptoniphilus</i> sp. gpac148	AM176535
<i>Peptoniphilus</i> sp. JC140	JF824803
<i>Peptoniphilus</i> sp. oral taxon 386	ADCS01000031
<i>Peptoniphilus</i> sp. oral taxon 836	AEAA01000090
<i>Peptostreptococcaceae bacterium ph1</i>	JN837495
<i>Peptostreptococcus anaerobius</i>	AY326462

<i>Peptostreptococcus micros</i>	AM176538
<i>Peptostreptococcus sp. 9succ1</i>	X90471
<i>Peptostreptococcus sp. oral clone AP24</i>	AB175072
<i>Peptostreptococcus sp. oral clone FJ023</i>	AY349390
<i>Peptostreptococcus sp. P4P_31 P3</i>	AY207059
<i>Peptostreptococcus stomatis</i>	ADGQ01000048
<i>Porphyromonadaceae bacterium NML 060648</i>	EF184292
<i>Porphyromonas asaccharolytica</i>	AENO01000048
<i>Porphyromonas endodontalis</i>	ACNN01000021
<i>Porphyromonas gingivalis</i>	AE015924
<i>Porphyromonas levii</i>	NR_025907
<i>Porphyromonas macacae</i>	NR_025908
<i>Porphyromonas somerae</i>	AB547667
<i>Porphyromonas sp. oral clone BB134</i>	AY005068
<i>Porphyromonas sp. oral clone F016</i>	AY005069
<i>Porphyromonas sp. oral clone P2PB_52 P1</i>	AY207054
<i>Porphyromonas sp. oral clone P4GB_100 P2</i>	AY207057
<i>Porphyromonas sp. UQD 301</i>	EU012301
<i>Porphyromonas uenonis</i>	ACLR01000152
<i>Prevotella albensis</i>	NR_025300
<i>Prevotella amnii</i>	AB547670
<i>Prevotella bergensis</i>	ACKS01000100
<i>Prevotella bivia</i>	ADFO01000096
<i>Prevotella brevis</i>	NR_041954
<i>Prevotella buccae</i>	ACRB01000001
<i>Prevotella buccalis</i>	JN867261
<i>Prevotella copri</i>	ACBX02000014
<i>Prevotella corporis</i>	L16465
<i>Prevotella dentalis</i>	AB547678
<i>Prevotella denticola</i>	CP002589
<i>Prevotella disiens</i>	AEDO01000026
<i>Prevotella genomosp. C1</i>	AY278624
<i>Prevotella genomosp. C2</i>	AY278625
<i>Prevotella genomosp. P7 oral clone MB2_P31</i>	DQ003620
<i>Prevotella genomosp. P8 oral clone MB3_P13</i>	DQ003622
<i>Prevotella genomosp. P9 oral clone MB7_G16</i>	DQ003633
<i>Prevotella heparinolytica</i>	GQ422742
<i>Prevotella histicola</i>	JN867315
<i>Prevotella intermedia</i>	AF414829
<i>Prevotella loescheii</i>	JN867231
<i>Prevotella maculosa</i>	AGEK01000035
<i>Prevotella marshii</i>	AEEI01000070
<i>Prevotella melaninogenica</i>	CP002122

<i>Prevotella micans</i>	AGWK01000061
<i>Prevotella multifformis</i>	AEWX01000054
<i>Prevotella multisaccharivorax</i>	AFJE01000016
<i>Prevotella nanceiensis</i>	JN867228
<i>Prevotella nigrescens</i>	AFPX01000069
<i>Prevotella oralis</i>	AEPE01000021
<i>Prevotella oris</i>	ADDV01000091
<i>Prevotella oulorum</i>	L16472
<i>Prevotella pallens</i>	AFPY01000135
<i>Prevotella ruminicola</i>	CP002006
<i>Prevotella salivae</i>	AB108826
<i>Prevotella sp. BI_42</i>	AJ581354
<i>Prevotella sp. CM38</i>	HQ610181
<i>Prevotella sp. ICM1</i>	HQ616385
<i>Prevotella sp. ICM55</i>	HQ616399
<i>Prevotella sp. JCM 6330</i>	AB547699
<i>Prevotella sp. oral clone AA020</i>	AY005057
<i>Prevotella sp. oral clone ASCG10</i>	AY923148
<i>Prevotella sp. oral clone ASCG12</i>	DQ272511
<i>Prevotella sp. oral clone AU069</i>	AY005062
<i>Prevotella sp. oral clone CY006</i>	AY005063
<i>Prevotella sp. oral clone DA058</i>	AY005065
<i>Prevotella sp. oral clone FL019</i>	AY349392
<i>Prevotella sp. oral clone FU048</i>	AY349393
<i>Prevotella sp. oral clone FW035</i>	AY349394
<i>Prevotella sp. oral clone GI030</i>	AY349395
<i>Prevotella sp. oral clone GI032</i>	AY349396
<i>Prevotella sp. oral clone GI059</i>	AY349397
<i>Prevotella sp. oral clone GU027</i>	AY349398
<i>Prevotella sp. oral clone HF050</i>	AY349399
<i>Prevotella sp. oral clone ID019</i>	AY349400
<i>Prevotella sp. oral clone IDR_CEC_0055</i>	AY550997
<i>Prevotella sp. oral clone IK053</i>	AY349401
<i>Prevotella sp. oral clone IK062</i>	AY349402
<i>Prevotella sp. oral clone P4PB_83 P2</i>	AY207050
<i>Prevotella sp. oral taxon 292</i>	GQ422735
<i>Prevotella sp. oral taxon 299</i>	ACWZ01000026
<i>Prevotella sp. oral taxon 300</i>	GU409549
<i>Prevotella sp. oral taxon 302</i>	ACZK01000043
<i>Prevotella sp. oral taxon 310</i>	GQ422737
<i>Prevotella sp. oral taxon 317</i>	ACQH01000158
<i>Prevotella sp. oral taxon 472</i>	ACZS01000106
<i>Prevotella sp. oral taxon 781</i>	GQ422744

<i>Prevotella sp. oral taxon 782</i>	GQ422745
<i>Prevotella sp. oral taxon F68</i>	HM099652
<i>Prevotella sp. oral taxon G60</i>	GU432133
<i>Prevotella sp. oral taxon G70</i>	GU432179
<i>Prevotella sp. oral taxon G71</i>	GU432180
<i>Prevotella sp. SEQ053</i>	JN867222
<i>Prevotella sp. SEQ065</i>	JN867234
<i>Prevotella sp. SEQ072</i>	JN867238
<i>Prevotella sp. SEQ116</i>	JN867246
<i>Prevotella sp. SG12</i>	GU561343
<i>Prevotella sp. sp24</i>	AB003384
<i>Prevotella sp. sp34</i>	AB003385
<i>Prevotella stercorea</i>	AB244774
<i>Prevotella tanneriae</i>	ACIJ02000018
<i>Prevotella timonensis</i>	ADEF01000012
<i>Prevotella veroralis</i>	ACVA01000027
<i>Prevotellaceae bacterium P4P_62 P1</i>	AY207061
<i>Propionibacteriaceae bacterium NML 02_0265</i>	EF599122
<i>Propionibacterium acidipropionici</i>	NC_019395
<i>Propionibacterium acnes</i>	ADJM01000010
<i>Propionibacterium avidum</i>	AJ003055
<i>Propionibacterium freudenreichii</i>	NR_036972
<i>Propionibacterium granulosum</i>	FJ785716
<i>Propionibacterium jensenii</i>	NR_042269
<i>Propionibacterium propionicum</i>	NR_025277
<i>Propionibacterium sp. 434_HC2</i>	AFIL01000035
<i>Propionibacterium sp. H456</i>	AB177643
<i>Propionibacterium sp. LG</i>	AY354921
<i>Propionibacterium sp. oral taxon 192</i>	GQ422728
<i>Propionibacterium sp. S555a</i>	AB264622
<i>Propionibacterium thoenii</i>	NR_042270
<i>Pseudomonas aeruginosa</i>	AABQ07000001
<i>Pseudomonas fluorescens</i>	AY622220
<i>Pseudomonas gessardii</i>	FJ943496
<i>Pseudomonas mendocina</i>	AAUL01000021
<i>Pseudomonas monteilii</i>	NR_024910
<i>Pseudomonas poae</i>	GU188951
<i>Pseudomonas pseudoalcaligenes</i>	NR_037000
<i>Pseudomonas putida</i>	AF094741
<i>Pseudomonas sp. 2_1_26</i>	ACWU01000257
<i>Pseudomonas sp. G1229</i>	DQ910482
<i>Pseudomonas sp. NP522b</i>	EU723211
<i>Pseudomonas stutzeri</i>	AM905854

<i>Pseudomonas tolaasii</i>	AF320988
<i>Pseudomonas viridiflava</i>	NR_042764
<i>Ralstonia pickettii</i>	NC_010682
<i>Ralstonia</i> sp. 5_7_47FAA	ACUF01000076
<i>Roseburia cecicola</i>	GU233441
<i>Roseburia faecalis</i>	AY804149
<i>Roseburia faecis</i>	AY305310
<i>Roseburia hominis</i>	AJ270482
<i>Roseburia intestinalis</i>	FP929050
<i>Roseburia inulinivorans</i>	AJ270473
<i>Roseburia</i> sp. 11SE37	FM954975
<i>Roseburia</i> sp. 11SE38	FM954976
<i>Rothia aeria</i>	DQ673320
<i>Rothia dentocariosa</i>	ADDW01000024
<i>Rothia mucilaginoso</i>	ACVO01000020
<i>Rothia nasimurium</i>	NR_025310
<i>Rothia</i> sp. oral taxon 188	GU470892
<i>Ruminobacter amylophilus</i>	NR_026450
<i>Ruminococcaceae bacterium D16</i>	ADDX01000083
<i>Ruminococcus albus</i>	AY445600
<i>Ruminococcus bromii</i>	EU266549
<i>Ruminococcus callidus</i>	NR_029160
<i>Ruminococcus champanellensis</i>	FP929052
<i>Ruminococcus flavefaciens</i>	NR_025931
<i>Ruminococcus gnavus</i>	X94967
<i>Ruminococcus hansenii</i>	M59114
<i>Ruminococcus lactaris</i>	ABOU02000049
<i>Ruminococcus obeum</i>	AY169419
<i>Ruminococcus</i> sp. 18P13	AJ515913
<i>Ruminococcus</i> sp. 5_1_39BFAA	ACII01000172
<i>Ruminococcus</i> sp. 9SE51	FM954974
<i>Ruminococcus</i> sp. ID8	AY960564
<i>Ruminococcus</i> sp. K_1	AB222208
<i>Ruminococcus torques</i>	AAVP02000002
<i>Salmonella bongori</i>	NR_041699
<i>Salmonella enterica</i>	NC_011149
<i>Salmonella enterica</i>	NC_011205
<i>Salmonella enterica</i>	DQ344532
<i>Salmonella enterica</i>	ABEH02000004
<i>Salmonella enterica</i>	ABAK02000001
<i>Salmonella enterica</i>	NC_011080
<i>Salmonella enterica</i>	EU118094
<i>Salmonella enterica</i>	NC_011094

<i>Salmonella enterica</i>	AE014613
<i>Salmonella enterica</i>	ABFH02000001
<i>Salmonella enterica</i>	ABEM01000001
<i>Salmonella enterica</i>	ABAM02000001
<i>Salmonella typhimurium</i>	DQ344533
<i>Salmonella typhimurium</i>	AF170176
<i>Selenomonas artemidis</i>	HM596274
<i>Selenomonas diana</i>	GQ422719
<i>Selenomonas flueggei</i>	AF287803
<i>Selenomonas genomsp. C1</i>	AY278627
<i>Selenomonas genomsp. C2</i>	AY278628
<i>Selenomonas genomsp. P5</i>	AY341820
<i>Selenomonas genomsp. P6 oral clone MB3_C41</i>	DQ003636
<i>Selenomonas genomsp. P7 oral clone MB5_C08</i>	DQ003627
<i>Selenomonas genomsp. P8 oral clone MB5_P06</i>	DQ003628
<i>Selenomonas infelix</i>	AF287802
<i>Selenomonas noxia</i>	GU470909
<i>Selenomonas ruminantium</i>	NR_075026
<i>Selenomonas sp. FOBRC9</i>	HQ616378
<i>Selenomonas sp. oral clone FT050</i>	AY349403
<i>Selenomonas sp. oral clone GI064</i>	AY349404
<i>Selenomonas sp. oral clone GT010</i>	AY349405
<i>Selenomonas sp. oral clone HU051</i>	AY349406
<i>Selenomonas sp. oral clone IK004</i>	AY349407
<i>Selenomonas sp. oral clone IQ048</i>	AY349408
<i>Selenomonas sp. oral clone JI021</i>	AY349409
<i>Selenomonas sp. oral clone JS031</i>	AY349410
<i>Selenomonas sp. oral clone OH4A</i>	AY947498
<i>Selenomonas sp. oral clone P2PA_80 P4</i>	AY207052
<i>Selenomonas sp. oral taxon 137</i>	AENV01000007
<i>Selenomonas sp. oral taxon 149</i>	AEEJ01000007
<i>Selenomonas sputigena</i>	ACKP02000033
<i>Serratia fonticola</i>	NR_025339
<i>Serratia liquefaciens</i>	NR_042062
<i>Serratia marcescens</i>	GU826157
<i>Serratia odorifera</i>	ADBY01000001
<i>Serratia proteamaculans</i>	AAUN01000015
<i>Shigella boydii</i>	AAKA01000007
<i>Shigella dysenteriae</i>	NC_007606
<i>Shigella flexneri</i>	AE005674
<i>Shigella sonnei</i>	NC_007384
<i>Sphingobacterium faecium</i>	NR_025537
<i>Sphingobacterium mizutaii</i>	JF708889

<i>Sphingobacterium multivorum</i>	NR_040953
<i>Sphingobacterium spiritivorum</i>	ACHA02000013
<i>Sphingomonas echinoides</i>	NR_024700
<i>Sphingomonas sp. oral clone FI012</i>	AY349411
<i>Sphingomonas sp. oral clone FZ016</i>	AY349412
<i>Sphingomonas sp. oral taxon A09</i>	HM099639
<i>Sphingomonas sp. oral taxon F71</i>	HM099645
<i>Staphylococcaceae bacterium NML 92_0017</i>	AY841362
<i>Staphylococcus aureus</i>	CP002643
<i>Staphylococcus auricularis</i>	JQ624774
<i>Staphylococcus capitis</i>	ACFR01000029
<i>Staphylococcus caprae</i>	ACRH01000033
<i>Staphylococcus carnosus</i>	NR_075003
<i>Staphylococcus cohnii</i>	JN175375
<i>Staphylococcus condimenti</i>	NR_029345
<i>Staphylococcus epidermidis</i>	ACHE01000056
<i>Staphylococcus equorum</i>	NR_027520
<i>Staphylococcus fleurettii</i>	NR_041326
<i>Staphylococcus haemolyticus</i>	NC_007168
<i>Staphylococcus hominis</i>	AM157418
<i>Staphylococcus lugdunensis</i>	AEQA01000024
<i>Staphylococcus pasteurii</i>	FJ189773
<i>Staphylococcus pseudintermedius</i>	CP002439
<i>Staphylococcus saccharolyticus</i>	NR_029158
<i>Staphylococcus saprophyticus</i>	NC_007350
<i>Staphylococcus sciuri</i>	NR_025520
<i>Staphylococcus sp. clone bottae7</i>	AF467424
<i>Staphylococcus sp. H292</i>	AB177642
<i>Staphylococcus sp. H780</i>	AB177644
<i>Staphylococcus succinus</i>	NR_028667
<i>Staphylococcus vitulinus</i>	NR_024670
<i>Staphylococcus warneri</i>	ACPZ01000009
<i>Staphylococcus xylosus</i>	AY395016
<i>Streptobacillus moniliformis</i>	NR_027615
<i>Streptococcus agalactiae</i>	AAJO01000130
<i>Streptococcus alactolyticus</i>	NR_041781
<i>Streptococcus anginosus</i>	AECT01000011
<i>Streptococcus australis</i>	AEQR01000024
<i>Streptococcus bovis</i>	AEEL01000030
<i>Streptococcus canis</i>	AJ413203
<i>Streptococcus constellatus</i>	AY277942
<i>Streptococcus cristatus</i>	AEVC01000028
<i>Streptococcus downei</i>	AEKN01000002

<i>Streptococcus dysgalactiae</i>	AP010935
<i>Streptococcus equi</i>	CP001129
<i>Streptococcus equinus</i>	AEVB01000043
<i>Streptococcus gallolyticus</i>	FR824043
<i>Streptococcus genomosp. C1</i>	AY278629
<i>Streptococcus genomosp. C2</i>	AY278630
<i>Streptococcus genomosp. C3</i>	AY278631
<i>Streptococcus genomosp. C4</i>	AY278632
<i>Streptococcus genomosp. C5</i>	AY278633
<i>Streptococcus genomosp. C6</i>	AY278634
<i>Streptococcus genomosp. C7</i>	AY278635
<i>Streptococcus genomosp. C8</i>	AY278609
<i>Streptococcus gordonii</i>	NC_009785
<i>Streptococcus infantarius</i>	ABJK02000017
<i>Streptococcus infantis</i>	AFNN01000024
<i>Streptococcus intermedius</i>	NR_028736
<i>Streptococcus lutetiensis</i>	NR_037096
<i>Streptococcus massiliensis</i>	AY769997
<i>Streptococcus milleri</i>	X81023
<i>Streptococcus mitis</i>	AM157420
<i>Streptococcus mutans</i>	AP010655
<i>Streptococcus oligofermentans</i>	AY099095
<i>Streptococcus oralis</i>	ADMV01000001
<i>Streptococcus parasanguinis</i>	AEKM01000012
<i>Streptococcus pasteurianus</i>	AP012054
<i>Streptococcus peroris</i>	AEVF01000016
<i>Streptococcus pneumoniae</i>	AE008537
<i>Streptococcus porcinus</i>	EF121439
<i>Streptococcus pseudopneumoniae</i>	FJ827123
<i>Streptococcus pseudoporcinus</i>	AENS01000003
<i>Streptococcus pyogenes</i>	AE006496
<i>Streptococcus rattus</i>	X58304
<i>Streptococcus salivarius</i>	AGBV01000001
<i>Streptococcus sanguinis</i>	NR_074974
<i>Streptococcus sinensis</i>	AF432857
<i>Streptococcus sp. 16362</i>	JN590019
<i>Streptococcus sp. 2_1_36FAA</i>	ACOI01000028
<i>Streptococcus sp. 2285_97</i>	AJ131965
<i>Streptococcus sp. 69130</i>	X78825
<i>Streptococcus sp. AC15</i>	HQ616356
<i>Streptococcus sp. ACS2</i>	HQ616360
<i>Streptococcus sp. AS20</i>	HQ616366
<i>Streptococcus sp. BS35a</i>	HQ616369

<i>Streptococcus</i> sp. C150	ACRI01000045
<i>Streptococcus</i> sp. CM6	HQ616372
<i>Streptococcus</i> sp. CM7	HQ616373
<i>Streptococcus</i> sp. ICM10	HQ616389
<i>Streptococcus</i> sp. ICM12	HQ616390
<i>Streptococcus</i> sp. ICM2	HQ616386
<i>Streptococcus</i> sp. ICM4	HQ616387
<i>Streptococcus</i> sp. ICM45	HQ616394
<i>Streptococcus</i> sp. M143	ACRK01000025
<i>Streptococcus</i> sp. M334	ACRL01000052
<i>Streptococcus</i> sp. OBRC6	HQ616352
<i>Streptococcus</i> sp. oral clone ASB02	AY923121
<i>Streptococcus</i> sp. oral clone ASCA03	DQ272504
<i>Streptococcus</i> sp. oral clone ASCA04	AY923116
<i>Streptococcus</i> sp. oral clone ASCA09	AY923119
<i>Streptococcus</i> sp. oral clone ASCB04	AY923123
<i>Streptococcus</i> sp. oral clone ASCB06	AY923124
<i>Streptococcus</i> sp. oral clone ASCC04	AY923127
<i>Streptococcus</i> sp. oral clone ASCC05	AY923128
<i>Streptococcus</i> sp. oral clone ASCC12	DQ272507
<i>Streptococcus</i> sp. oral clone ASCD01	AY923129
<i>Streptococcus</i> sp. oral clone ASCD09	AY923130
<i>Streptococcus</i> sp. oral clone ASCD10	DQ272509
<i>Streptococcus</i> sp. oral clone ASCE03	AY923134
<i>Streptococcus</i> sp. oral clone ASCE04	AY953253
<i>Streptococcus</i> sp. oral clone ASCE05	DQ272510
<i>Streptococcus</i> sp. oral clone ASCE06	AY923135
<i>Streptococcus</i> sp. oral clone ASCE09	AY923136
<i>Streptococcus</i> sp. oral clone ASCE10	AY923137
<i>Streptococcus</i> sp. oral clone ASCE12	AY923138
<i>Streptococcus</i> sp. oral clone ASCF05	AY923140
<i>Streptococcus</i> sp. oral clone ASCF07	AY953255
<i>Streptococcus</i> sp. oral clone ASCF09	AY923142
<i>Streptococcus</i> sp. oral clone ASCG04	AY923145
<i>Streptococcus</i> sp. oral clone BW009	AY005042
<i>Streptococcus</i> sp. oral clone CH016	AY005044
<i>Streptococcus</i> sp. oral clone GK051	AY349413
<i>Streptococcus</i> sp. oral clone GM006	AY349414
<i>Streptococcus</i> sp. oral clone P2PA_41 P2	AY207051
<i>Streptococcus</i> sp. oral clone P4PA_30 P4	AY207064
<i>Streptococcus</i> sp. oral taxon 071	AEEP01000019
<i>Streptococcus</i> sp. oral taxon G59	GU432132
<i>Streptococcus</i> sp. oral taxon G62	GU432146

<i>Streptococcus</i> sp. oral taxon G63	GU432150
<i>Streptococcus</i> sp. SHV515	Y07601
<i>Streptococcus suis</i>	FM252032
<i>Streptococcus thermophilus</i>	CP000419
<i>Streptococcus uberis</i>	HQ391900
<i>Streptococcus urinalis</i>	DQ303194
<i>Streptococcus vestibularis</i>	AEKO01000008
<i>Streptococcus viridans</i>	AF076036
<i>Sutterella morbirenis</i>	AJ832129
<i>Sutterella parvirubra</i>	AB300989
<i>Sutterella sanguinis</i>	AJ748647
<i>Sutterella</i> sp. YIT 12072	AB491210
<i>Sutterella stercoricanis</i>	NR_025600
<i>Sutterella wadsworthensis</i>	ADMF01000048
<i>Synergistes genomsp. C1</i>	AY278615
<i>Synergistes</i> sp. RMA 14551	DQ412722
<i>Synergistetes bacterium</i> ADV897	GQ258968
<i>Synergistetes bacterium</i> LBVCM1157	GQ258969
<i>Synergistetes bacterium</i> oral taxon 362	GU410752
<i>Synergistetes bacterium</i> oral taxon D48	GU430992
<i>Turicibacter sanguinis</i>	AF349724
<i>Veillonella atypica</i>	AEDS01000059
<i>Veillonella dispar</i>	ACIK02000021
<i>Veillonella genomsp. P1 oral clone</i> MB5_P17	DQ003631
<i>Veillonella montpellierensis</i>	AF473836
<i>Veillonella parvula</i>	ADFU01000009
<i>Veillonella</i> sp. 3_1_44	ADCV01000019
<i>Veillonella</i> sp. 6_1_27	ADCW01000016
<i>Veillonella</i> sp. ACP1	HQ616359
<i>Veillonella</i> sp. AS16	HQ616365
<i>Veillonella</i> sp. BS32b	HQ616368
<i>Veillonella</i> sp. ICM51a	HQ616396
<i>Veillonella</i> sp. MSA12	HQ616381
<i>Veillonella</i> sp. NVG 100cf	EF108443
<i>Veillonella</i> sp. OK11	JN695650
<i>Veillonella</i> sp. oral clone ASCA08	AY923118
<i>Veillonella</i> sp. oral clone ASCB03	AY923122
<i>Veillonella</i> sp. oral clone ASCG01	AY923144
<i>Veillonella</i> sp. oral clone ASCG02	AY953257
<i>Veillonella</i> sp. oral clone OH1A	AY947495
<i>Veillonella</i> sp. oral taxon 158	AENU01000007
<i>Veillonellaceae bacterium</i> oral taxon 131	GU402916
<i>Veillonellaceae bacterium</i> oral taxon 155	GU470897

<i>Vibrio cholerae</i>	AAUR01000095
<i>Vibrio fluvialis</i>	X76335
<i>Vibrio furnissii</i>	CP002377
<i>Vibrio mimicus</i>	ADAF01000001
<i>Vibrio parahaemolyticus</i>	AAWQ01000116
<i>Vibrio sp. RC341</i>	ACZT01000024
<i>Vibrio vulnificus</i>	AE016796
<i>Yersinia aldovae</i>	AJ871363
<i>Yersinia aleksiciae</i>	AJ627597
<i>Yersinia bercovieri</i>	AF366377
<i>Yersinia enterocolitica</i>	FR729477
<i>Yersinia frederiksenii</i>	AF366379
<i>Yersinia intermedia</i>	AF366380
<i>Yersinia kristensenii</i>	ACCA01000078
<i>Yersinia mollaretii</i>	NR_027546
<i>Yersinia pestis</i>	AE013632
<i>Yersinia pseudotuberculosis</i>	NC_009708
<i>Yersinia rohdei</i>	ACCD01000071

Table 3: Exemplary Bacterial Strains

Strain	Deposit Number
<i>Parabacteroides goldsteinii</i>	PTA-126574
<i>Bifidobacterium animalis ssp. lactis Strain A</i>	PTA-125097
<i>Blautia Massiliensis Strain A</i>	PTA-125134
<i>Prevotella Strain B</i>	NRRL accession Number B 50329
<i>Prevotella Histicola</i>	PTA-126140
<i>Blautia Strain A</i>	PTA-125346
<i>Lactococcus lactis cremoris Strain A</i>	PTA-125368
<i>Lactobacillus salivarius</i>	PTA-125893
<i>Ruminococcus gnavus strain</i>	PTA-125706
<i>Tyzzerella nexilis strain</i>	PTA-125707
<i>Paraclostridium benzoelyticum</i>	PTA-125894
<i>Ruminococcus gnavus (also referred to as Mediterraneibacter gnavus)</i>	PTA-126695
<i>Veillonella parvula</i>	PTA-125710
<i>Veillonella atypica Strain A</i>	PTA-125709
<i>Veillonella atypica Strain B</i>	PTA-125711
<i>Veillonella parvula Strain A</i>	PTA-125691
<i>Veillonella parvula Strain B</i>	PTA-125711
<i>Veillonella tobetsuensis Strain A</i>	PTA-125708
<i>Agathobaculum sp.</i>	PTA-125892
<i>Turicibacter sanguinis</i>	PTA-125889
<i>Klebsiella quasipneumoniae subsp. similipneumoniae</i>	PTA-125891
<i>Klebsiella oxytoca</i>	PTA-125890
<i>Megasphaera Sp. Strain A</i>	PTA-126770
<i>Megasphaera Sp.</i>	PTA-126837
<i>Harryflintia acetispora</i>	PTA-126694
<i>Fournierella massiliensis</i>	PTA-126696

Modified Bacteria and mEVs

[1533] In some aspects, the bacteria and/or mEVs (such as smEVs and/or pmEVs) described herein are modified such that they comprise, are linked to, and/or are bound by a therapeutic moiety.

[1534] In some embodiments, the therapeutic moiety is a cancer-specific moiety. In some embodiments, the cancer-specific moiety has binding specificity for a cancer cell (e.g., has binding specificity for a cancer-specific antigen). In some embodiments, the cancer-specific moiety comprises an antibody or antigen binding fragment thereof. In some embodiments, the cancer-specific moiety comprises a T cell receptor or a chimeric antigen receptor (CAR). In some embodiments, the cancer-specific moiety comprises a ligand for a receptor expressed on the surface of a cancer cell or a receptor-binding fragment thereof. In some embodiments, the cancer-specific moiety is a bipartite fusion protein that has two parts: a first part that binds to and/or is linked to the bacterium and a second part that is capable of binding to a cancer cell (e.g., by having binding specificity for a cancer-specific antigen). In some embodiments, the first part is a fragment of or a full-length peptidoglycan recognition protein, such as PGRP. In some embodiments the first part has binding specificity for the mEV (e.g., by having binding specificity for a bacterial antigen). In some embodiments, the first and/or second part comprises an antibody or antigen binding fragment thereof. In some embodiments, the first and/or second part comprises a T cell receptor or a chimeric antigen receptor (CAR). In some embodiments, the first and/or second part comprises a ligand for a receptor expressed on the surface of a cancer cell or a receptor-binding fragment thereof. In certain embodiments, co-administration of the cancer-specific moiety with the pharmaceutical agent (either in combination or in separate administrations) increases the targeting of the pharmaceutical agent to the cancer cells.

[1535] In some embodiments, the bacteria and/or mEVs described herein can be modified such that they comprise, are linked to, and/or are bound by a magnetic and/or paramagnetic moiety (e.g., a magnetic bead). In some embodiments, the magnetic and/or paramagnetic moiety is comprised by and/or directly linked to the bacteria. In some embodiments, the magnetic and/or paramagnetic moiety is linked to and/or a part of a bacteria- or an mEV-binding moiety that binds to the bacteria or mEV. In some embodiments, the bacteria- or mEV-binding moiety is a fragment of or a full-length

peptidoglycan recognition protein, such as PGRP. In some embodiments the bacteria- or mEV-binding moiety has binding specificity for the bacteria or mEV (e.g., by having binding specificity for a bacterial antigen). In some embodiments, the bacteria- or mEV-binding moiety comprises an antibody or antigen binding fragment thereof. In some embodiments, the bacteria- or mEV-binding moiety comprises a T cell receptor or a chimeric antigen receptor (CAR). In some embodiments, the bacteria- or mEV-binding moiety comprises a ligand for a receptor expressed on the surface of a cancer cell or a receptor-binding fragment thereof. In certain embodiments, co-administration of the magnetic and/or paramagnetic moiety with the bacteria or mEVs (either together or in separate administrations) can be used to increase the targeting of the mEVs (e.g., to cancer cells and/or a part of a subject where cancer cells are present).

Production of Processed Microbial Extracellular Vesicles (pmEVs)

[1536] In certain aspects, the pmEVs described herein can be prepared using any method known in the art.

[1537] In some embodiments, the pmEVs are prepared without a pmEV purification step. For example, in some embodiments, bacteria from which the pmEVs described herein are released are killed using a method that leaves the bacterial pmEVs intact, and the resulting bacterial components, including the pmEVs, are used in the methods and compositions described herein. In some embodiments, the bacteria are killed using an antibiotic (e.g., using an antibiotic described herein). In some embodiments, the bacteria are killed using UV irradiation.

[1538] In some embodiments, the pmEVs described herein are purified from one or more other bacterial components. Methods for purifying pmEVs from bacteria (and optionally, other bacterial components) are known in the art. In some embodiments, pmEVs are prepared from bacterial cultures using methods described in Thein, *et al.* (*J. Proteome Res.* 9(12):6135-6147 (2010)) or Sandrini, *et al.* (*Bio-protocol* 4(21): e1287 (2014)), each of which is hereby incorporated by reference in its entirety. In some embodiments, the bacteria are cultured to high optical density and then centrifuged to pellet bacteria (e.g., at 10,000- 15,000 x g for 10- 15 min at room temperature or 4°C). In some embodiments, the supernatants are discarded and cell pellets are frozen at -80°C. In some embodiments, cell pellets are thawed on ice and resuspended in 100 mM Tris-HCl, pH 7.5 supplemented with 1 mg/mL DNase I. In some embodiments, cells are lysed using an Emulsiflex C-3 (Avestin,

Inc.) under conditions recommended by the manufacturer. In some embodiments, debris and unlysed cells are pelleted by centrifugation at 10,000 x g for 15 min at 4°C. In some embodiments, supernatants are then centrifuged at 120,000 x g for 1 hour at 4°C. In some embodiments, pellets are resuspended in ice-cold 100 mM sodium carbonate, pH 11, incubated with agitation for 1 hr at 4°C, and then centrifuged at 120,000 x g for 1 hour at 4°C. In some embodiments, pellets are resuspended in 100 mM Tris-HCl, pH 7.5, re-centrifuged at 120,000 x g for 20 min at 4°C, and then resuspended in 0.1 M Tris-HCl, pH 7.5 or in PBS. In some embodiments, samples are stored at -20°C.

[1539] In certain aspects, pmEVs are obtained by methods adapted from Sandrini et al, 2014. In some embodiments, bacterial cultures are centrifuged at 10,000-15,500 x g for 10-15 min at room temp or at 4°C. In some embodiments, cell pellets are frozen at -80°C and supernatants are discarded. In some embodiments, cell pellets are thawed on ice and resuspended in 10 mM Tris-HCl, pH 8.0, 1 mM EDTA supplemented with 0.1 mg/mL lysozyme. In some embodiments, samples are incubated with mixing at room temp or at 37°C for 30 min. In some embodiments, samples are re-frozen at -80°C and thawed again on ice. In some embodiments, DNase I is added to a final concentration of 1.6 mg/mL and MgCl₂ to a final concentration of 100 mM. In some embodiments, samples are sonicated using a QSonica Q500 sonicator with 7 cycles of 30 sec on and 30 sec off. In some embodiments, debris and unlysed cells are pelleted by centrifugation at 10,000 x g for 15 min. at 4°C. In some embodiments, supernatants are then centrifuged at 110,000 x g for 15 min at 4°C. In some embodiments, pellets are resuspended in 10 mM Tris-HCl, pH 8.0, 2% Triton X-100 and incubated 30-60 min with mixing at room temperature. In some embodiments, samples are centrifuged at 110,000 x g for 15 min at 4°C. In some embodiments, pellets are resuspended in PBS and stored at -20°C.

[1540] In certain aspects, a method of forming (e.g., preparing) isolated bacterial pmEVs, described herein, comprises the steps of: (a) centrifuging a bacterial culture, thereby forming a first pellet and a first supernatant, wherein the first pellet comprises cells; (b) discarding the first supernatant; (c) resuspending the first pellet in a solution; (d) lysing the cells; (e) centrifuging the lysed cells, thereby forming a second pellet and a second supernatant; (f) discarding the second pellet and centrifuging the second supernatant, thereby forming a third pellet and a third supernatant; (g) discarding the third supernatant and resuspending the third pellet in a second solution, thereby forming the isolated bacterial pmEVs.

[1541] In some embodiments, the method further comprises the steps of: (h) centrifuging the solution of step (g), thereby forming a fourth pellet and a fourth supernatant; (i) discarding the fourth supernatant and resuspending the fourth pellet in a third solution. In some embodiments, the method further comprises the steps of: (j) centrifuging the solution of step (i), thereby forming a fifth pellet and a fifth supernatant; and (k) discarding the fifth supernatant and resuspending the fifth pellet in a fourth solution.

[1542] In some embodiments, the centrifugation of step (a) is at 10,000 x g. In some embodiments the centrifugation of step (a) is for 10-15 minutes. In some embodiments, the centrifugation of step (a) is at 4 °C or room temperature. In some embodiments, step (b) further comprises freezing the first pellet at -80 °C. In some embodiments, the solution in step (c) is 100mM Tris-HCl, pH 7.5 supplemented with 1mg/ml DNaseI. In some embodiments, the solution in step (c) is 10mM Tris-HCl, pH 8.0, 1mM EDTA, supplemented with 0.1 mg/ml lysozyme. In some embodiments, step (c) further comprises incubating for 30 minutes at 37 °C or room temperature. In some embodiments, step (c) further comprises freezing the first pellet at -80 °C. In some embodiments, step (c) further comprises adding DNase I to a final concentration of 1.6mg/ml. In some embodiments, step (c) further comprises adding MgCl₂ to a final concentration of 100mM. In some embodiments, the cells are lysed in step (d) via homogenization. In some embodiments, the cells are lysed in step (d) via emulsiflex C3. In some embodiments, the cells are lysed in step (d) via sonication. In some embodiments, the cells are sonicated in 7 cycles, wherein each cycle comprises 30 seconds of sonication and 30 seconds without sonication. In some embodiments, the centrifugation of step (e) is at 10,000 x g. In some embodiments, the centrifugation of step (e) is for 15 minutes. In some embodiments, the centrifugation of step (e) is at 4 °C or room temperature.

[1543] In some embodiments, the centrifugation of step (f) is at 120,000 x g. In some embodiments, the centrifugation of step (f) is at 110,000 x g. In some embodiments, the centrifugation of step (f) is for 1 hour. In some embodiments, the centrifugation of step (f) is for 15 minutes. In some embodiments, the centrifugation of step (f) is at 4 °C or room temperature. In some embodiments, the second solution in step (g) is 100 mM sodium carbonate, pH 11. In some embodiments, the second solution in step (g) is 10mM Tris-HCl pH 8.0, 2% triton X-100. In some embodiments, step (g) further comprises incubating the solution for 1 hour at 4 °C. In some embodiments, step (g) further comprises incubating the solution for 30-60 minutes at room temperature. In some embodiments, the centrifugation

of step (h) is at 120,000 x g. In some embodiments, the centrifugation of step (h) is at 110,000 x g. In some embodiments, the centrifugation of step (h) is for 1 hour. In some embodiments, the centrifugation of step (h) is for 15 minutes. In some embodiments, the centrifugation of step (h) is at 4 °C or room temperature. In some embodiments, the third solution in step (i) is 100mM Tris-HCl, pH 7.5. In some embodiments, the third solution in step (i) is PBS. In some embodiments, the centrifugation of step (j) is at 120,000 x g. In some embodiments, the centrifugation of step (j) is for 20 minutes. In some embodiments, the centrifugation of step (j) is at 4 °C or room temperature. In some embodiments, the fourth solution in step (k) is 100mM Tris-HCl, pH 7.5 or PBS.

[1544] pmEVs obtained by methods provided herein may be further purified by size based column chromatography, by affinity chromatography, and by gradient ultracentrifugation, using methods that may include, but are not limited to, use of a sucrose gradient or Optiprep gradient. Briefly, using a sucrose gradient method, if ammonium sulfate precipitation or ultracentrifugation were used to concentrate the filtered supernatants, pellets are resuspended in 60% sucrose, 30 mM Tris, pH 8.0. If filtration was used to concentrate the filtered supernatant, the concentrate is buffer exchanged into 60% sucrose, 30 mM Tris, pH 8.0, using an Amicon Ultra column. Samples are applied to a 35-60% discontinuous sucrose gradient and centrifuged at 200,000 x g for 3-24 hours at 4°C. Briefly, using an Optiprep gradient method, if ammonium sulfate precipitation or ultracentrifugation were used to concentrate the filtered supernatants, pellets are resuspended in 35% Optiprep in PBS. In some embodiments, if filtration was used to concentrate the filtered supernatant, the concentrate is diluted using 60% Optiprep to a final concentration of 35% Optiprep. Samples are applied to a 35-60% discontinuous sucrose gradient and centrifuged at 200,000 x g for 3-24 hours at 4°C.

[1545] In some embodiments, to confirm sterility and isolation of the pmEV preparations, pmEVs are serially diluted onto agar medium used for routine culture of the bacteria being tested, and incubated using routine conditions. Non-sterile preparations are passed through a 0.22 um filter to exclude intact cells. To further increase purity, isolated pmEVs may be DNase or proteinase K treated.

[1546] In some embodiments, the sterility of the pmEV preparations can be confirmed by plating a portion of the pmEVs onto agar medium used for standard culture of the bacteria used in the generation of the pmEVs and incubating using standard conditions.

[1547] In some embodiments select pmEVs are isolated and enriched by chromatography and binding surface moieties on pmEVs. In other embodiments, select pmEVs are isolated and/or enriched by fluorescent cell sorting by methods using affinity reagents, chemical dyes, recombinant proteins or other methods known to one skilled in the art.

[1548] The pmEVs can be analyzed, e.g., as described in Jeppesen, et al. Cell 177:428 (2019).

[1549] In some embodiments, pmEVs are lyophilized.

[1550] In some embodiments, pmEVs are gamma irradiated (e.g., at 17.5 or 25 kGy).

[1551] In some embodiments, pmEVs are UV irradiated.

[1552] In some embodiments, pmEVs are heat inactivated (e.g., at 50°C for two hours or at 90°C for two hours).

[1553] In some embodiments, pmEVs are acid treated.

[1554] In some embodiments, pmEVs are oxygen sparged (e.g., at 0.1 vvm for two hours).

[1555] The phase of growth can affect the amount or properties of bacteria. In the methods of pmEV preparation provided herein, pmEVs can be isolated, e.g., from a culture, at the start of the log phase of growth, midway through the log phase, and/or once stationary phase growth has been reached.

Production of Secreted Microbial Extracellular Vesicles (smEVs)

[1556] In certain aspects, the smEVs described herein can be prepared using any method known in the art.

[1557] In some embodiments, the smEVs are prepared without an smEV purification step. For example, in some embodiments, bacteria described herein are killed using a method that leaves the smEVs intact and the resulting bacterial components, including the smEVs, are used in the methods and compositions described herein. In some embodiments, the bacteria are killed using an antibiotic (e.g., using an antibiotic described herein). In some embodiments, the bacteria are killed using UV irradiation. In some embodiments, the bacteria are heat-killed.

[1558] In some embodiments, the smEVs described herein are purified from one or more other bacterial components. Methods for purifying smEVs from bacteria are known in

the art. In some embodiments, smEVs are prepared from bacterial cultures using methods described in S. Bin Park, et al. PLoS ONE. 6(3):e17629 (2011) or G. Norheim, et al. PLoS ONE. 10(9): e0134353 (2015) or Jeppesen, et al. Cell 177:428 (2019), each of which is hereby incorporated by reference in its entirety. In some embodiments, the bacteria are cultured to high optical density and then centrifuged to pellet bacteria (e.g., at 10,000 x g for 30 min at 4°C, at 15,500 x g for 15 min at 4°C). In some embodiments, the culture supernatants are then passed through filters to exclude intact bacterial cells (e.g., a 0.22 µm filter). In some embodiments, the supernatants are then subjected to tangential flow filtration, during which the supernatant is concentrated, species smaller than 100 kDa are removed, and the media is partially exchanged with PBS. In some embodiments, filtered supernatants are centrifuged to pellet bacterial smEVs (e.g., at 100,000-150,000 x g for 1-3 hours at 4°C, at 200,000 x g for 1-3 hours at 4°C). In some embodiments, the smEVs are further purified by resuspending the resulting smEV pellets (e.g., in PBS), and applying the resuspended smEVs to an Optiprep (iodixanol) gradient or gradient (e.g., a 30-60% discontinuous gradient, a 0-45% discontinuous gradient), followed by centrifugation (e.g., at 200,000 x g for 4-20 hours at 4°C). smEV bands can be collected, diluted with PBS, and centrifuged to pellet the smEVs (e.g., at 150,000 x g for 3 hours at 4°C, at 200,000 x g for 1 hour at 4°C). The purified smEVs can be stored, for example, at -80°C or -20°C until use. In some embodiments, the smEVs are further purified by treatment with DNase and/or proteinase K.

[1559] For example, in some embodiments, cultures of bacteria can be centrifuged at 11,000 x g for 20-40 min at 4°C to pellet bacteria. Culture supernatants may be passed through a 0.22 µm filter to exclude intact bacterial cells. Filtered supernatants may then be concentrated using methods that may include, but are not limited to, ammonium sulfate precipitation, ultracentrifugation, or filtration. For example, for ammonium sulfate precipitation, 1.5-3 M ammonium sulfate can be added to filtered supernatant slowly, while stirring at 4°C. Precipitations can be incubated at 4°C for 8-48 hours and then centrifuged at 11,000 x g for 20-40 min at 4°C. The resulting pellets contain bacteria smEVs and other debris. Using ultracentrifugation, filtered supernatants can be centrifuged at 100,000-200,000 x g for 1-16 hours at 4°C. The pellet of this centrifugation contains bacteria smEVs and other debris such as large protein complexes. In some embodiments, using a filtration technique, such as through the use of an Amicon Ultra spin filter or by tangential flow

filtration, supernatants can be filtered so as to retain species of molecular weight > 50 or 100 kDa.

[1560] Alternatively, smEVs can be obtained from bacteria cultures continuously during growth, or at selected time points during growth, for example, by connecting a bioreactor to an alternating tangential flow (ATF) system (e.g., XCell ATF from Repligen). The ATF system retains intact cells (>0.22 μm) in the bioreactor, and allows smaller components (e.g., smEVs, free proteins) to pass through a filter for collection. For example, the system may be configured so that the <0.22 μm filtrate is then passed through a second filter of 100 kDa, allowing species such as smEVs between 0.22 μm and 100 kDa to be collected, and species smaller than 100 kDa to be pumped back into the bioreactor. Alternatively, the system may be configured to allow for medium in the bioreactor to be replenished and/or modified during growth of the culture. smEVs collected by this method may be further purified and/or concentrated by ultracentrifugation or filtration as described above for filtered supernatants.

[1561] smEVs obtained by methods provided herein may be further purified by size-based column chromatography, by affinity chromatography, by ion-exchange chromatography, and by gradient ultracentrifugation, using methods that may include, but are not limited to, use of a sucrose gradient or Optiprep gradient. Briefly, using a sucrose gradient method, if ammonium sulfate precipitation or ultracentrifugation were used to concentrate the filtered supernatants, pellets are resuspended in 60% sucrose, 30 mM Tris, pH 8.0 . If filtration was used to concentrate the filtered supernatant, the concentrate is buffer exchanged into 60% sucrose, 30 mM Tris, pH 8.0 , using an Amicon Ultra column. Samples are applied to a 35 - 60% discontinuous sucrose gradient and centrifuged at $200,000 \times g$ for 3 - 24 hours at 4°C . Briefly, using an Optiprep gradient method, if ammonium sulfate precipitation or ultracentrifugation were used to concentrate the filtered supernatants, pellets are resuspended in PBS and 3 volumes of 60% Optiprep are added to the sample. In some embodiments, if filtration was used to concentrate the filtered supernatant, the concentrate is diluted using 60% Optiprep to a final concentration of 35% Optiprep. Samples are applied to a 0 - 45% discontinuous Optiprep gradient and centrifuged at $200,000 \times g$ for 3 - 24 hours at 4°C , e.g., 4 - 24 hours at 4°C .

[1562] In some embodiments, to confirm sterility and isolation of the smEV preparations, smEVs are serially diluted onto agar medium used for routine culture of the bacteria being tested, and incubated using routine conditions. Non-sterile preparations are

passed through a 0.22 μm filter to exclude intact cells. To further increase purity, isolated smEVs may be DNase or proteinase K treated.

[1563] In some embodiments, for preparation of smEVs used for in vivo injections, purified smEVs are processed as described previously (G. Norheim, et al. PLoS ONE. 10(9): e0134353 (2015)). Briefly, after sucrose gradient centrifugation, bands containing smEVs are resuspended to a final concentration of 50 $\mu\text{g/mL}$ in a solution containing 3% sucrose or other solution suitable for in vivo injection known to one skilled in the art. This solution may also contain adjuvant, for example aluminum hydroxide at a concentration of 0-0.5% (w/v). In some embodiments, for preparation of smEVs used for in vivo injections, smEVs in PBS are sterile-filtered to $< 0.22 \mu\text{m}$.

[1564] In certain embodiments, to make samples compatible with further testing (e.g., to remove sucrose prior to TEM imaging or in vitro assays), samples are buffer exchanged into PBS or 30 mM Tris, pH 8.0 using filtration (e.g., Amicon Ultra columns), dialysis, or ultracentrifugation ($200,000 \times g$, ≥ 3 hours, 4°C) and resuspension.

[1565] In some embodiments, the sterility of the smEV preparations can be confirmed by plating a portion of the smEVs onto agar medium used for standard culture of the bacteria used in the generation of the smEVs and incubating using standard conditions.

[1566] In some embodiments, select smEVs are isolated and enriched by chromatography and binding surface moieties on smEVs. In other embodiments, select smEVs are isolated and/or enriched by fluorescent cell sorting by methods using affinity reagents, chemical dyes, recombinant proteins or other methods known to one skilled in the art.

[1567] The smEVs can be analyzed, e.g., as described in Jeppesen, et al. Cell 177:428 (2019).

[1568] In some embodiments, smEVs are lyophilized.

[1569] In some embodiments, smEVs are gamma irradiated (e.g., at 17.5 or 25 kGy).

[1570] In some embodiments, smEVs are UV irradiated.

[1571] In some embodiments, smEVs are heat inactivated (e.g., at 50°C for two hours or at 90°C for two hours).

[1572] In some embodiments, smEVs are acid treated.

[1573] In some embodiments, smEVs are oxygen sparged (e.g., at 0.1 vvm for two hours).

[1574] The phase of growth can affect the amount or properties of bacteria and/or smEVs produced by bacteria. For example, in the methods of smEV preparation provided herein, smEVs can be isolated, e.g., from a culture, at the start of the log phase of growth, midway through the log phase, and/or once stationary phase growth has been reached.

[1575] The growth environment (e.g., culture conditions) can affect the amount of smEVs produced by bacteria. For example, the yield of smEVs can be increased by an smEV inducer, as provided in Table 4.

Table 4: Culture Techniques to Increase smEV Production

smEV inducement	smEV inducer	Acts on
Temperature		
	Heat RT to 37 °C temp change 37 to 40 °C temp change	stress response simulates infection febrile infection
ROS		
	Plumbagin Cumene hydroperoxide Hydrogen Peroxide	oxidative stress response oxidative stress response oxidative stress response
Antibiotics		
	Ciprofloxacin Gentamycin Polymyxin B D-cycloserine	bacterial SOS response protein synthesis outer membrane cell wall
Osmolyte		
	NaCl	osmotic stress
Metal Ion Stress		
	Iron Chelation EDTA Low Hemin	iron levels removes divalent cations iron levels
Media additives or removal		
	Lactate Amino acid deprivation Hexadecane Glucose Sodium bicarbonate PQS Diamines+ DFMO High nutrients	growth stress stress growth ToxT induction vesiculator (from bacteria) membrane anchoring (negativicutes only) enhanced growth

Other mechanisms	Low nutrients	
	Oxygen	oxygen stress in anaerobe
	No Cysteine	oxygen stress in anaerobe
	Inducing biofilm or flocculation	
	Diauxic Growth	
	Phage	
	Urea	

[1576] In the methods of smEVs preparation provided herein, the method can optionally include exposing a culture of bacteria to an smEV inducer prior to isolating smEVs from the bacterial culture. The culture of bacteria can be exposed to an smEV inducer at the start of the log phase of growth, midway through the log phase, and/or once stationary phase growth has been reached.

Solid Dosage Form Compositions

[1577] In certain embodiments, provided herein are solid dosage forms comprising a pharmaceutical agent that contains bacteria and/or mEVs (such as smEVs and/or pmEVs). In some embodiments, the pharmaceutical agent can optionally contain one or more additional components, such as a cryoprotectant. The pharmaceutical agent can be lyophilized (e.g., resulting in a powder). The pharmaceutical agent can be combined with one or more excipients (e.g., pharmaceutically acceptable excipients) in the solid dosage form. In some embodiments, the pharmaceutical agent can be (or be present in) a medicinal product, medical food, a food product, or a dietary supplement.

[1578] In certain embodiments, provided herein are solid dosage forms comprising a pharmaceutical agent that contains bacteria. The bacteria can be live bacteria (e.g., powder or biomass thereof); non-live (dead) bacteria (e.g., powder or biomass thereof); non-replicating bacteria (e.g., powder or biomass thereof); gamma irradiated bacteria (e.g., powder or biomass thereof); and/or lyophilized bacteria (e.g., powder or biomass thereof).

[1579] In certain embodiments, provided herein are solid dosage forms comprising a pharmaceutical agent that contains mEVs. The mEVs can be from culture media (e.g., culture supernatant). The mEVs can be from live bacteria (e.g., powder or biomass thereof); the mEVs can be from non-live (dead) bacteria (e.g., powder or biomass thereof); the mEVs can be from non-replicating bacteria (e.g., powder or biomass thereof); the mEVs can be

from gamma irradiated bacteria (e.g., powder or biomass thereof); and/or the mEVs can be from lyophilized bacteria (e.g., powder or biomass thereof).

[1580] In some embodiments, the pharmaceutical agent comprises mEVs substantially or entirely free of bacteria (e.g., whole bacteria) (e.g., live bacteria, dead (e.g., killed) bacteria, non-replicating bacteria, attenuated bacteria. In some embodiments, the pharmaceutical agents comprise both mEVs and bacteria (e.g., whole bacteria) (e.g., live bacteria, killed bacteria, attenuated bacteria). In some embodiments, the pharmaceutical agents comprise bacteria and/or mEVs from one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) of the bacteria strains or species listed herein. In some embodiments, the pharmaceutical agents comprise bacteria and/or mEVs from one of the bacteria strains or species listed herein. In some embodiments, the pharmaceutical agents comprise lyophilized bacteria and/or mEVs. In some embodiments, the pharmaceutical agent comprises gamma irradiated bacteria and/or mEVs. The mEVs (such as smEVs and/or pmEVs) can be gamma irradiated after the mEVs are isolated (e.g., prepared).

[1581] In some embodiments, to quantify the numbers of mEVs (such as smEVs and/or pmEVs) and/or bacteria present in a sample, electron microscopy (e.g., EM of ultrathin frozen sections) can be used to visualize the mEVs (such as smEVs and/or pmEVs) and/or bacteria and count their relative numbers. Alternatively, nanoparticle tracking analysis (NTA), Coulter counting, or dynamic light scattering (DLS) or a combination of these techniques can be used. NTA and the Coulter counter count particles and show their sizes. DLS gives the size distribution of particles, but not the concentration. Bacteria frequently have diameters of 1-2 μm (microns). The full range is 0.2-20 μm . Combined results from Coulter counting and NTA can reveal the numbers of bacteria and/or mEVs (such as smEVs and/or pmEVs) in a given sample. Coulter counting reveals the numbers of particles with diameters of 0.7-10 μm . For most bacterial and/or mEV (such as smEV and/or pmEV) samples, the Coulter counter alone can reveal the number of bacteria and/or mEVs (such as smEVs and/or pmEVs) in a sample. pmEVs are 20-600 nm in diameter. For NTA, a Nanosight instrument can be obtained from Malvern Pananalytical. For example, the NS300 can visualize and measure particles in suspension in the size range 10-2000nm. NTA allows for counting of the numbers of particles that are, for example, 50-1000 nm in diameter. DLS reveals the distribution of particles of different diameters within an approximate range of 1 nm – 3 μm .

[1582] mEVs can be characterized by analytical methods known in the art (e.g., Jeppesen, et al. Cell 177:428 (2019)).

[1583] In some embodiments, the bacteria and/or mEVs may be quantified based on particle count. For example, particle count of a bacteria and/or mEV preparation can be measured using NTA.

[1584] In some embodiments, the bacteria and/or mEVs may be quantified based on the amount of protein, lipid, or carbohydrate. For example, total protein content of a bacteria and/or preparation can be measured using the Bradford assay or BCA.

[1585] In some embodiments, mEVs are isolated away from one or more other bacterial components of the source bacteria or bacterial culture. In some embodiments, bacteria are isolated away from one or more other bacterial components of the source bacterial culture. In some embodiments, the pharmaceutical agent further comprises other bacterial components.

[1586] In certain embodiments, the mEV preparation obtained from the source bacteria may be fractionated into subpopulations based on the physical properties (e.g., sized, density, protein content, binding affinity) of the subpopulations. One or more of the mEV subpopulations can then be incorporated into the pharmaceutical agents of the invention.

[1587] In certain aspects, provided herein are solid dosage forms comprising pharmaceutical agents that comprise bacteria and/or mEVs (such as smEVs and/or pmEVs) useful for the treatment and/or prevention of disease (e.g., a cancer, an autoimmune disease, an inflammatory disease, or a metabolic disease), as well as methods of making and/or identifying such bacteria and/or mEVs, and methods of using pharmaceutical agents and solid dosage forms thereof (e.g., for the treatment of a cancer, an autoimmune disease, an inflammatory disease, or a metabolic disease, either alone or in combination with other therapeutics). In some embodiments, the pharmaceutical agents comprise both mEVs (such as smEVs and/or pmEVs) and bacteria (e.g., whole bacteria) (e.g., live bacteria, dead (e.g., killed) bacteria, non-replicating bacteria, attenuated bacteria). In some embodiments, the pharmaceutical agents comprise bacteria in the absence of mEVs (such as smEVs and/or pmEVs). In some embodiments, the pharmaceutical agents comprise mEVs (such as smEVs and/or pmEVs) in the absence of bacteria. In some embodiments, the pharmaceutical agents comprise mEVs (such as smEVs and/or pmEVs) and/or bacteria from one or more of the bacteria strains or species listed herein. In some embodiments, the pharmaceutical agents

comprise mEVs (such as smEVs and/or pmEVs) and/or bacteria from one of the bacteria strains or species listed herein.

[1588] In certain aspects, provided are pharmaceutical agents for administration to a subject (e.g., human subject). In some embodiments, the pharmaceutical agents are combined with additional active and/or inactive materials in order to produce a final product, which may be in single dosage unit or in a multi-dose format. In some embodiments, the pharmaceutical agent is combined with an adjuvant such as an immuno-adjuvant (e.g., a STING agonist, a TLR agonist, or a NOD agonist).

[1589] In some embodiments, the solid dosage form comprises at least one carbohydrate.

[1590] In some embodiments, the solid dosage form comprises at least one lipid. In some embodiments, the lipid comprises at least one fatty acid selected from lauric acid (12:0), myristic acid (14:0), palmitic acid (16:0), palmitoleic acid (16:1), margaric acid (17:0), heptadecenoic acid (17:1), stearic acid (18:0), oleic acid (18:1), linoleic acid (18:2), linolenic acid (18:3), octadecatetraenoic acid (18:4), arachidic acid (20:0), eicosenoic acid (20:1), eicosadienoic acid (20:2), eicosatetraenoic acid (20:4), eicosapentaenoic acid (20:5) (EPA), docosanoic acid (22:0), docosenoic acid (22:1), docosapentaenoic acid (22:5), docosahexaenoic acid (22:6) (DHA), and tetracosanoic acid (24:0).

[1591] In some embodiments, the solid dosage form comprises at least one supplemental mineral or mineral source. Examples of minerals include, without limitation: chloride, sodium, calcium, iron, chromium, copper, iodine, zinc, magnesium, manganese, molybdenum, phosphorus, potassium, and selenium. Suitable forms of any of the foregoing minerals include soluble mineral salts, slightly soluble mineral salts, insoluble mineral salts, chelated minerals, mineral complexes, non-reactive minerals such as carbonyl minerals, and reduced minerals, and combinations thereof.

[1592] In some embodiments, the solid dosage form comprises at least one vitamin. The at least one vitamin can be fat-soluble or water-soluble vitamins. Suitable vitamins include but are not limited to vitamin C, vitamin A, vitamin E, vitamin B12, vitamin K, riboflavin, niacin, vitamin D, vitamin B6, folic acid, pyridoxine, thiamine, pantothenic acid, and biotin. Suitable forms of any of the foregoing are salts of the vitamin, derivatives of the vitamin, compounds having the same or similar activity of the vitamin, and metabolites of the vitamin.

[1593] In some embodiments, the solid dosage form comprises an excipient. Non-limiting examples of suitable excipients include a buffering agent, a preservative, a stabilizer, a binder, a compaction agent, a lubricant, a dispersion enhancer, a disintegration agent, a flavoring agent, a sweetener, and a coloring agent.

[1594] Suitable excipients that can be included in the solid dosage form can be one or more pharmaceutically acceptable excipients known in the art. For example, see Rowe, Sheskey, and Quinn, eds., *Handbook of Pharmaceutical Excipients*, sixth ed.; 2009; Pharmaceutical Press and American Pharmacists Association.

Solid Dosage Forms

[1595] The solid dosage form described herein can be, e.g., a tablet or a minitab. Further, a plurality of minitab. can be in (e.g., loaded into) a capsule.

[1596] In certain embodiments, the solid dosage form comprises a capsule. In some embodiments, the capsule is a size 00, size 0, size 1, size 2, size 3, size 4, or size 5 capsule. In some embodiments, the capsule is a size 0 capsule. As used herein, the size of the capsule refers to the size of the tablet prior to application of an enteric coating. In some embodiments, the capsule is banded after loading (and prior to enterically coating the capsule). In some embodiments, the capsule is banded with an HPMC-based banding solution.

[1597] In some embodiments, the solid dosage form comprises a tablet (> 4mm) (e.g., 5mm-17mm). For example, the tablet is a 5mm, 6mm, 7mm, 8mm, 9mm, 10mm, 11mm, 12mm, 13mm, 14mm, 15mm, 16mm, 17mm, or 18mm tablet. The size refers to the diameter of the tablet, as is known in the art. As used herein, the size of the tablet refers to the size of the tablet prior to application of an enteric coating.

[1598] In some embodiments, the solid dosage form comprises a minitab. The minitab. can be in the size range of 1mm-4 mm range. E.g., the minitab. can be a 1mm minitab., 1.5 mm minitab., 2mm minitab., 3mm minitab., or 4mm minitab. The size refers to the diameter of the minitab., as is known in the art. As used herein, the size of the minitab. refers to the size of the minitab. prior to application of an enteric coating.

[1599] The minitab. can be in a capsule. The capsule can be a size 00, size 0, size 1, size 2, size 3, size 4, or size 5 capsule. The capsule that contains the minitab. can comprise HPMC (hydroxyl propyl methyl cellulose) or gelatin. The minitab. can be

inside a capsule: the number of minitabets inside a capsule will depend on the size of the capsule and the size of the minitabets. As an example, a size 0 capsule can contain 31-35 (an average of 33) minitabets that are 3mm minitabets. In some embodiments, the capsule is banded after loading. In some embodiments, the capsule is banded with an HPMC-based banding solution.

Coating:

[1600] The solid dosage form (e.g., capsule, tablet or minitab) described herein can be enterically coated, e.g., with one enteric coating layer or with two layers of enteric coating, e.g., an inner enteric coating and an outer enteric coating. The inner enteric coating and outer enteric coating are not identical (e.g., the inner enteric coating and outer enteric coating do not contain the same components in the same amounts). The enteric coating allows for release of the pharmaceutical agent, e.g., in the small intestine.

[1601] Release of the pharmaceutical agent in the small intestine allows the pharmaceutical agent to target and affect cells (e.g., epithelial cells and/or immune cells) located at these specific locations, e.g., which can cause a local effect in the gastrointestinal tract and/or cause a systemic effect (e.g., an effect outside of the gastrointestinal tract).

[1602] EUDRAGIT is the brand name for a diverse range of polymethacrylate-based copolymers. It includes anionic, cationic, and neutral copolymers based on methacrylic acid and methacrylic/acrylic esters or their derivatives.

[1603] Examples of other materials that can be used in the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) include cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), poly(vinyl acetate phthalate) (PVAP), hydroxypropyl methylcellulose phthalate (HPMCP), fatty acids, waxes, shellac (esters of gallic acid), plastics, plant fibers, zein, Aqua-Zein® (an aqueous zein formulation containing no alcohol), amylose starch, starch derivatives, dextrans, methyl acrylate-methacrylic acid copolymers, cellulose acetate succinate, hydroxypropyl methyl cellulose acetate succinate (hypromellose acetate succinate), methyl methacrylate-methacrylic acid copolymers, and/or sodium alginate.

[1604] The enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) can include a methacrylic acid ethyl acrylate (MAE) copolymer (1:1).

[1605] The one enteric coating can include methacrylic acid ethyl acrylate (MAE) copolymer (1:1) (such as Kollicoat MAE 100P).

[1606] The one enteric coating can include a Eudragit copolymer, e.g., a Eudragit L (e.g., Eudragit L 100-55; Eudragit L 30 D-55), a Eudragit S, a Eudragit RL, a Eudragit RS, a Eudragit E, or a Eudragit FS (e.g., Eudragit FS 30 D).

[1607] Other examples of materials that can be used in the enteric coating (e.g., the one enteric coating or the inner enteric coating and/or the outer enteric coating) include those described in, e.g., U.S. 6312728; U.S. 6623759; U.S. 4775536; U.S. 5047258; U.S. 5292522; U.S. 6555124; U.S. 6638534; U.S. 2006/0210631; U.S. 2008/200482; U.S. 2005/0271778; U.S. 2004/0028737; WO 2005/044240.

[1608] See also, e.g., U.S. 9233074, which provides pH dependent, enteric polymers that can be used with the solid dosage forms provided herein, including methacrylic acid copolymers, polyvinylacetate phthalate, hydroxypropylmethyl cellulose acetate succinate, hydroxypropylmethyl cellulose phthalate and cellulose acetate phthalate; suitable methacrylic acid copolymers include: poly(methacrylic acid, methyl methacrylate) 1:1 sold, for example, under the Eudragit L100 trade name; poly(methacrylic acid, ethyl acrylate) 1:1 sold, for example, under the Eudragit L100-55 trade name; partially-neutralized poly(methacrylic acid, ethyl acrylate) 1:1 sold, for example, under the Kollicoat MAE-100P trade name; and poly(methacrylic acid, methyl methacrylate) 1:2 sold, for example, under the Eudragit S100 trade name.

[1609] In some embodiments, the solid dosage form comprises a sub-coat, e.g., under the enteric coating (e.g., one enteric coating). The sub-coat can be used, e.g., to visually mask the appearance of the pharmaceutical agent.

Dose

[1610] The dose of the pharmaceutical agent (e.g., for human subjects) is the dose per capsule or tablet or per total number of minitablets used in a capsule.

[1611] In embodiments where dose is determined by total cell count, total cell count can be determined by Coulter counter.

[1612] In some embodiments, the pharmaceutical agent comprises bacteria and the dose of bacteria is about 1×10^7 to about 2×10^{12} (e.g., about 3×10^{10} or about 1.5×10^{11} or about 1.5×10^{12}) cells (e.g., wherein cell number is determined by total cell count, which is determined by Coulter counter), wherein the dose is per capsule or tablet or per total

number of minitabets in a capsule. In some embodiments, the pharmaceutical agent comprises bacteria and the dose of bacteria is about 1×10^{10} to about 2×10^{12} (e.g., about 1.6×10^{11} or about 8×10^{11} or about 9.6×10^{11} or about 12.8×10^{11} or about 1.6×10^{12}) cells (e.g., wherein cell number is determined by total cell count, which is determined by Coulter counter), wherein the dose is per capsule or tablet or per total number of minitabets in a capsule.

[1613] In some embodiments, the pharmaceutical agent comprises bacteria and the dose of bacteria is about 1×10^9 , about 3×10^9 , about 5×10^9 , about 1.5×10^{10} , about 3×10^{10} , about 5×10^{10} , about 1.5×10^{11} , about 1.5×10^{12} , or about 2×10^{12} cells, wherein the dose is per capsule or tablet or per total number of minitabets in a capsule.

[1614] In some embodiments, the pharmaceutical agent comprises mEVs and the dose of mEVs is about 1×10^5 to about 7×10^{13} particles (e.g., wherein particle count is determined by NTA (nanoparticle tracking analysis)), wherein the dose is per capsule or tablet or per total number of minitabets in a capsule. In some embodiments, the pharmaceutical agent comprises mEVs and the dose of mEVs is about 1×10^{10} to about 7×10^{13} particles (e.g., wherein particle count is determined by NTA (nanoparticle tracking analysis)), wherein the dose is per capsule or tablet or per total number of minitabets in a capsule.

[1615] In some embodiments, wherein the pharmaceutical agent comprises mEVs, the dose of mEVs is about 2×10^6 to about 2×10^{16} particles (e.g., wherein particle count is determined by NTA (nanoparticle tracking analysis)), wherein the dose is per capsule or tablet or per total number of minitabets in a capsule.

[1616] The solid dosage form allows higher efficacy if used at the same dose as in powder form; and/or allows a reduced dose (e.g., 1/10 lower dose) for similar efficacy as when the pharmaceutical agent is used in powder form.

[1617] In some embodiments, wherein the pharmaceutical agent comprises bacteria, the dose can be approximately 1/10 dose for similar efficacy as when the pharmaceutical agent is used in powder form and the dose can be about 3×10^9 or about 1.5×10^{10} cells per dose.

[1618] The solid dosage form can allow higher efficacy if used at the same dose of the pharmaceutical agent as in a powder formulation.

[1619] In some embodiments, the pharmaceutical agent dose can be a milligram (mg) dose determined by weight the pharmaceutical agent. The dose of the pharmaceutical agent is per capsule or tablet or per total number of minitabets, e.g., in a capsule.

[1620] For example, to administer a 1x dose of the pharmaceutical agent of about 400 mg, about 200 mg of the pharmaceutical agent is present per capsule and two capsules are administered, resulting in a dose of about 400 mg. The two capsules can be administered, for example, 1x or 2x daily.

[1621] As another example, to obtain similar efficacy as a powder form of the pharmaceutical agent, the dose of pharmaceutical agent can be reduced by 1/10 when prepared as a solid dosage form described herein (e.g., by enterically coating a tablet or minitabets containing the pharmaceutical agent).

[1622] For example, for a minitabets: about 0.1 to about 3.5 mg (0.1, 0.35, 1.0, 3.5 mg) of the pharmaceutical agent can be contained per minitabets. The minitabets can be inside a capsule: the number of minitabets inside a capsule will depend on the size of the capsule and the size of the minitabets. For example, an average of 33 (range of 31-35) 3mm minitabets fit inside a size 0 capsule. As an example, 0.1- 3.5 mg of the pharmaceutical agent per minitabets, the dose range will be 3.3 mg- 115.5 mg (for 33 minitabets in size 0 capsule) per capsule (3.1 mg- 108.5 mg for 31 minitabets in size 0 capsule) (3.5 mg- 122.5 mg for 35 minitabets in size 0 capsule). Multiple capsules and/or larger capsule(s) can be administered to increase the administered dose and/or can be administered one or more times per day to increase the administered dose.

[1623] In some embodiments, the dose can be about 3 mg to about 125 mg of the pharmaceutical agent, per capsule or tablet or per total number of minitabets, e.g., in a capsule.

[1624] In some embodiments, the dose can be about 35 mg to about 1200 mg (e.g., about 35 mg, about 125 mg, about 350 mg, or about 1200 mg) of the pharmaceutical agent.

[1625] In some embodiments, the dose of the pharmaceutical agent can be about 30 mg to about 3500 mg (about 25, about 50, about 75, about 100, about 150, about 250, about 300, about 350, about 400, about 500, about 600, about 750, about 1000, about 1250, about 1300, about 2000, about 2500, about 3000, or about 3500 mg).

[1626] A human dose can be calculated appropriately based on allometric scaling of a dose administered to a model organism (e.g., mouse).

[1627] In some embodiments, one or two tablets capsules can be administered one or two times a day.

[1628] The pharmaceutical agent contains the bacteria and/or mEVs and can also contain one or more additional components, such as cryoprotectants, stabilizers, etc.

[1629] In some embodiments, the mg (by weight) dose of the pharmaceutical agent is, e.g., about 1 mg to about 500 mg per capsule, or per tablet, or per total number of minitables, e.g., used in a capsule.

Methods of Use

[1630] The solid dosage forms described herein allow, e.g., for oral administration of a pharmaceutical agent contained therein.

[1631] The solid dosage forms described herein can provide an increase in therapeutic efficacy and/or physiological effect as compared to other dosage forms (e.g., non-enterically coated dosage forms (e.g., non-minitabiet non-enterically coated dosage forms, or non-tablet non-enterically coated dosage forms) or a suspension of biomass or powder).

[1632] The solid dosage forms described herein can provide release in the small intestine of the pharmaceutical agent contained in the solid dosage form.

[1633] The solid dosage forms described herein can provide release of the pharmaceutical agent in the small intestine, e.g., to deliver the pharmaceutical agent that can act on immune cells and/or epithelial cells in the small intestine, e.g., to cause a systemic effect (e.g., an effect outside of the gastrointestinal tract) and/or a local effect in the gastrointestinal tract.

[1634] The solid dosage forms described herein can provide increased efficacy and/or physiological effect (as measured by a systemic effect (e.g., outside of the gastrointestinal tract) of the pharmaceutical agent, e.g., in ear thickness in a DTH model for inflammation; tumor size in cancer model), e.g., as compared to oral gavage of the same dose of pharmaceutical agent.

[1635] The solid dosage forms described herein can be used in the treatment and/or prevention of a cancer, inflammation, autoimmunity, or a metabolic condition.

[1636] Methods of using a solid dosage form (e.g., for oral administration) (e.g., for pharmaceutical use) comprising a pharmaceutical agent (e.g., a therapeutically effective amount thereof), wherein the pharmaceutical agent comprises bacteria and/or microbial

extracellular vesicles (mEVs), and wherein the solid dosage form is enterically coated are described herein.

[1637] The methods and administered solid dosage forms described herein allow, e.g., for oral administration of a pharmaceutical agent contained therein. The solid dosage form can be administered to a subject in a fed or fasting state. The solid dosage form can be administered, e.g., on an empty stomach (e.g., one hour before eating or two hours after eating). The solid dosage form can be administered one hour before eating. The solid dosage form can be administered two hours after eating.

[1638] The methods and administered solid dosage forms described herein can provide an increase in therapeutic efficacy and/or physiological effect as compared to other dosage forms (e.g., non-enterically coated dosage forms (e.g., non-minitabiet non-enterically coated dosage forms, or non-tablet non-enterically coated dosage forms) or a suspension of biomass or powder).

[1639] The methods and administered solid dosage forms described herein can provide release in the small intestine of the pharmaceutical agent contained in the solid dosage form.

[1640] The methods and administered solid dosage forms described herein can provide release of the pharmaceutical agent in the small intestine, e.g., to deliver the pharmaceutical agent that can act on immune cells and/or epithelial cells in the small intestine, e.g., to cause a systemic effect (e.g., an effect outside of the gastrointestinal tract) and/or a local effect in the gastrointestinal tract.

[1641] The methods and administered solid dosage forms described herein can provide increased efficacy and/or physiological effect (as measured by a systemic effect (e.g., outside of the gastrointestinal tract) of the pharmaceutical agent, e.g., in ear thickness in a DTH model for inflammation; tumor size in cancer model), e.g., as compared to oral gavage of the same dose of pharmaceutical agent.

[1642] The methods and administered solid dosage forms described herein can be used in the treatment and/or prevention of a cancer, inflammation, autoimmunity, dysbiosis, or a metabolic condition.

[1643] A solid dosage form for use in the treatment and/or prevention of a cancer, inflammation, autoimmunity, dysbiosis, or a metabolic condition is provided herein.

[1644] Use of a solid dosage form for the preparation of a medicament for the treatment and/or prevention of a cancer, inflammation, autoimmunity, dysbiosis, or a metabolic condition is provided herein.

Method of Making Solid Dosage Forms

[1645] The disclosure also provides methods of making a solid dosage form (e.g., for oral administration) (e.g., for pharmaceutical use) that comprises a pharmaceutical agent. The pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs). The pharmaceutical agent can also contain one or more additional components (e.g., a cryoprotectant). The solid dosage form is enterically coated.

[1646] A method of making the solid dosage form can include:

[1647] Loading the pharmaceutical agent into a capsule; and

[1648] Coating the capsule with one or two layers of enteric coating (e.g., with an enteric coating or inner enteric coating and outer enteric coating as described herein), thereby preparing an enterically coated capsule, and thereby preparing the solid dosage form;

[1649] Optionally combining the pharmaceutical agent with a pharmaceutically acceptable excipient prior to loading into the capsule; and/or

[1650] Optionally banding the capsule after loading the capsule (e.g., optionally banding the capsule after loading the capsule and prior to enterically coating the capsule).

[1651] A method of making the solid dosage form can include:

[1652] Compressing a pharmaceutical agent described herein into a minitab; and

[1653] Coating the minitab with one or two layers of enteric coating (e.g., with an enteric coating or inner enteric coating and outer enteric coating as described herein), thereby preparing an enterically coated minitab;

[1654] Optionally filling a capsule with a plurality of enterically coated minitabs, thereby preparing the solid dosage form.

[1655] A method of making the solid dosage form can include:

[1656] Compressing a pharmaceutical agent described herein into a tablet; and

[1657] Coating the tablet with one or two layers of enteric coating (e.g., with an enteric coating or inner enteric coating and outer enteric coating as described herein), thereby preparing enterically coated tablet, and thereby preparing the solid dosage form.

[1658] A method of making the solid dosage form can include a method for preparing an enterically coated capsule comprising a pharmaceutical agent (e.g., a therapeutically effective amount thereof), wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), the method comprising:

[1659] a) loading the pharmaceutical agent into a capsule; and

[1660] b) enterically coating the capsule (e.g., with an enteric coating or inner enteric coating and outer enteric coating as described herein), thereby preparing the enterically coated capsule (thereby preparing the solid dosage form).

[1661] A method of making the solid dosage form can include a method for preparing an enterically coated capsule comprising a pharmaceutical agent (e.g., a therapeutically effective amount thereof), wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), the method comprising:

[1662] a) combining the pharmaceutical agent with a pharmaceutically acceptable excipient;

[1663] b) loading the pharmaceutical agent and pharmaceutically acceptable excipient into a capsule; and

[1664] c) enterically coating the capsule (e.g., with an enteric coating or inner enteric coating and outer enteric coating as described herein), thereby preparing the enterically coated capsule (thereby preparing the solid dosage form).

[1665] A method of making the solid dosage form can include a method for preparing an enterically coated capsule comprising a pharmaceutical agent (e.g., a therapeutically effective amount thereof), wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), the method comprising:

[1666] a) loading the pharmaceutical agent into a capsule;

[1667] b) banding the capsule; and

[1668] c) enterically coating the capsule (e.g., with an enteric coating or inner enteric coating and outer enteric coating as described herein), thereby preparing the enterically coated capsule (thereby preparing the solid dosage form).

[1669] A method of making the solid dosage form can include a method for preparing an enterically coated capsule comprising a pharmaceutical agent (e.g., a therapeutically effective amount thereof), wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), the method comprising:

[1670] a) combining the pharmaceutical agent with a pharmaceutically acceptable excipient;

[1671] b) loading the pharmaceutical agent and pharmaceutically acceptable excipient into a capsule;

[1672] c) banding the capsule; and

[1673] d) enterically coating the capsule (e.g., with an enteric coating or inner enteric coating and outer enteric coating as described herein), thereby preparing the enterically coated capsule (thereby preparing the solid dosage form).

[1674] A method of making the solid dosage form can include a method for preparing an enterically coated tablet comprising a pharmaceutical agent (e.g., a therapeutically effective amount thereof), wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), the method comprising:

[1675] a) combining the pharmaceutical agent with a pharmaceutically acceptable excipient;

[1676] b) compressing the pharmaceutical agent and pharmaceutically acceptable excipient, thereby forming a tablet; and

[1677] c) enterically coating the tablet (e.g., with an enteric coating or inner enteric coating and outer enteric coating as described herein), thereby preparing the enterically coated tablet (thereby preparing the solid dosage form).

[1678] A method of making the solid dosage form can include a method for preparing an enterically coated minitabket comprising a pharmaceutical agent (e.g., a therapeutically effective amount thereof), wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), the method comprising:

[1679] a) combining the pharmaceutical agent with a pharmaceutically acceptable excipient;

[1680] b) compressing the pharmaceutical agent and pharmaceutically acceptable excipient, thereby forming a minitabket; and

[1681] c) enterically coating the minitabket (e.g., with an enteric coating or inner enteric coating and outer enteric coating as described herein), thereby preparing the enterically coated minitabket (thereby preparing the solid dosage form). Optionally, the minitabket is loaded into a capsule.

[1682] A method of making the solid dosage form can include a method for preparing a capsule comprising enterically coated minitabkets comprising a pharmaceutical

agent (e.g., a therapeutically effective amount thereof), wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), the method comprising:

[1683] a) combining the pharmaceutical agent with a pharmaceutically acceptable excipient;

[1684] b) compressing the pharmaceutical agent and pharmaceutically acceptable excipient, thereby forming a minitab;let;

[1685] c) enterically coating the minitab;let (e.g., with an enteric coating or inner enteric coating and outer enteric coating as described herein), and

[1686] d) loading the capsule with enterically coated minitab;lets,

[1687] thereby preparing the capsule (thereby preparing the solid dosage form).

Additional Aspects of the Solid Dosage Forms

[1688] The solid dosage forms, e.g., as described herein, comprising a pharmaceutical agent (e.g., a therapeutically effective amount thereof), wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), and wherein the solid dosage form is enterically coated, can provide a therapeutically effective amount of the pharmaceutical agent to a subject, e.g., a human.

[1689] The solid dosage forms, e.g., as described herein, comprising a pharmaceutical agent (e.g., a therapeutically effective amount thereof), wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), and wherein the solid dosage form is enterically coated, can provide a non-natural amount of the therapeutically effective components (e.g., present in the pharmaceutical agent) to a subject, e.g., a human.

[1690] The solid dosage forms, e.g., as described herein, comprising a pharmaceutical agent (e.g., a therapeutically effective amount thereof), wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), and wherein the solid dosage form is enterically coated, can provide an unnatural quantity of the therapeutically effective components (e.g., present in the pharmaceutical agent) to a subject, e.g., a human.

[1691] The solid dosage forms, e.g., as described herein, comprising a pharmaceutical agent (e.g., a therapeutically effective amount thereof), wherein the therapeutic agent comprises bacteria and/or microbial extracellular vesicles (mEVs), and

wherein the solid dosage form is enterically coated, can bring about one or more changes to a subject, e.g., human, e.g., to treat or prevent a disease or a health disorder.

[1692] The solid dosage forms, e.g., as described herein, comprising a pharmaceutical agent (e.g., a therapeutically effective amount thereof), wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), and wherein the solid dosage form is enterically coated, has potential for significant utility, e.g., to affect a subject, e.g., a human, e.g., to treat or prevent a disease or a health disorder.

Other Content of Solid Dosage Forms

[1693] The solid dosage forms described herein (e.g., enterically coated tablets or minitables) can be used to deliver an additional pharmaceutical agent (e.g., in place of, or in addition to, a pharmaceutical agent that comprises bacteria and/or mEVs (e.g., as defined herein)), such as a small molecule, vitamin or mineral supplement, or dietary supplement, to the small intestine.

[1694] Additional pharmaceutical agents that contain a small molecule that can be prepared in a solid dosage form described herein include one or more of the following small molecules: analgesics, anti-inflammatories, anaesthetics, anticonvulsants, antidiabetic agents, antihistamines, anti-infectives, antineoplastics, antiparkinsonian agents, antirheumatic agents, appetite stimulants, appetite suppressants, blood modifiers, bone metabolism modifiers, cardiovascular agents, central nervous system depressants, central nervous system stimulants, decongestants, dopamine receptor agonists, electrolytes, gastrointestinal agents, immunomodulators, muscle relaxants, narcotics, parasympathomimetics, sympathomimetics, sedatives, and hypnotics; pirenzepine, misoprostol, ursodeoxycholic acid, Alosetron, Cilansetron, Mosapride, Prucalopride, Tegaserod, Metoclopramide, Bromopride, Clebopride, Domperidone, Alizapride, Cinitapride, Cisapride, Codeine, Morphine, loperamide, diphenoxylate, methylnaltrexone bromide, Valerian, and mannitol; Antispasmodics selected from the group consisting of atropine sulphate, dicycloverine hydrochloride, hyoscine butylbromine, propantheline bromide, alverine citrate, and mebeverine hydrochloride; Motility stimulants selected from the group consisting of metoclopramide and domperidone; H₂-Receptor antagonists selected from the group consisting of Cimetidine, famotidine, nizatidine, and ranitidine; Antimuscarinics; Chelates selected from the group consisting of Tripotassium dicitratbismuthate and sucralfate; Prostaglandin analogues; Aminosalicylates selected from

the group consisting of balsazide sodium, mesalazine, olsalazine, and sulphasalazine; Corticosteroids selected from the group consisting of beclometasone dipropionate, budesonide, hydrocortisone, and prednisolone; Affecting immune response selected from the group consisting of ciclosporin, mercaptopurine, methotrexate, adalimumab, and infliximab; Stimulant Laxatives selected from the group consisting of bisacodyl, dantron, docusate, and sodium picosulfate; Drugs affecting biliary composition and flow; Bile acids sequestrants selected from the group consisting of colestyramine, Oxyphenyclimine, Camylofin, Mebeverine, Trimebutine, Rociverine, Dicycloverine, Dihexyverine, Difemerine, Piperidolate, Benzilone, Mepenzolate, Pipenzolate, Glycopyrronium, Oxyphenonium, Penthienate, Methantheline, Propantheline, Otilonium bromide, Tridihexethyl, Isopropamide, Hexocyclium, Poldine, Bevonium, Diphemanil, Tiemonium iodide, Prifinium bromide, Timepidium bromide, Fenpiverinium, Papaverine, Drotaverine, Moxaverine, 5-HT₃ antagonists, 5-HT₄ agonists, Fenpiprane, Diisopromine, Chlorbenzoxamine, Pinaverium, Fenoverine, Idanpramine, Proxazole, Alverine, Trepibutone, Isometheptene, Caroverine, Phloroglucinol, Silicones, Trimethyldiphenylpropylamine, Atropine, Hyoscyamine, Scopolamine, Butylscopolamine, Methylscopolamine, Methylatropine, Fentonium, Cimetropium bromide, and primarily dopamine antagonists; Proton pump inhibitors selected from the group consisting of Omeprazole, lansoprazole, pantoprazole, esomeprazole, and rabeprazole sodium; Opioids and opioid receptor antagonists; Analgesics selected from the group consisting of Acetaminophen, Diclofenac, Diflunisal, Etodolac, Fenoprofen, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Ketorolac, Meclofenamate, Mefenamic Acid, Meloxicam, Nabumetone, Naproxen, Oxaprozin, Phenylbutazone, Piroxicam, Sulindac, Tolmetin, Celecoxib, Buprenorphine, Butorphanol, Codeine, Hydrocodone, Hydromorphone, Levorphanol, Meperidine, Methadone, Morphine, Nalbuphine, Oxycodone, Oxymorphone, Pentazocine, Propoxyphene, and Tramadol; Sleep drugs selected from the group consisting of Nitrazepam, Flurazepam, Loprazolam, Lormetazepam, Temazepam, Zaleplon, Zolpidem, Zopiclone, Chloral Hydrate, Triclofos, Clomethiazole, Quazepam, triazolam, Estazolam, Clonazepam, Alprazolam, Eszopiclone, Rozerem, Trazodone, Amitriptyline, Doxepin, Benzodiazepine drugs, melatonin, diphenhydramine, and herbal remedies; Cardiac glycosides selected from the group consisting of Digoxin and digitoxin; Phosphodiesterase inhibitors selected from the group consisting of enoximone and milrinone; Thiazides and related diuretics selected from the group consisting of bendroflumethiazide, chlortalidone,

cyclopenthiiazide, inapamide, metolazone, and xipamide; Diuretics selected from the group consisting of furosemide, bumetanide, and torasemide; Potassium sparing diuretics and aldosterone antagonists selected from the group consisting of amiloride hydrochloride, triamterene, weplerenone, and spironolactone; Osmotic diuretics; Drugs for arrhythmias selected from the group consisting of adenosine, amiodarone hydrochloride, disopyramide, flecainide acetate, propafenone hydrochloride, and lidocaine hydrochloride; Beta adrenoreceptor blocking drugs selected from the group consisting of propranolol, atenolol, acebutolol, bisoprolol fumarate, carvedilol, celiprolol, esmolol, lebatolol, metoprolol tartrate, nadolol, nebivolol, oxprenolol, pindolol, solatol, and timolol; Hypertension drugs selected from the group consisting of ambrisentan, bosentan, diazoxide, hydralazine, iloprost, minoxidil, sildenafil, sitaxentan, sodium nitroprusside, clonidine, methyldopa, moxonidine, guanethidine monosulphate, doxazosin, indoramin, prazosin, terazosin, phenoxybenzamine, and phentolamine mesilate; Drugs affecting the renin-angiotensin system selected from the group consisting of Captopril, Cilazapril, Enalapril Maleate, Fosinopril, Imidapril, Lisinopril, Moexipril, Perindopril Erbumine, Quinapril, Ramipril, Trandolapril, Candesartan Cilexetil, Eprosartan, Irbesartan, Losartan, Olmesartan Medoxomil, Telmisartan, Valsartan, and Aliskiren; Nitrates, calcium channel Blockers, and antianginal drugs selected from the group consisting of Glyceryl trinitrate, Isosorbide Dinitrate, Isosorbide Mononitrate, Amlodipine, Diltiazem, Felodipine, Isradipine, Lacidipine, Lercanidipine, Nicardipine, Nifedipine, Nimodipine, Verapamil, Ivabradine, Nicorandil, and Ranolazine; Peripheral vasodilators and related drugs selected from the group consisting of Cilostazol, Inositol Nicotinate, Moxisylyte, Naftidrofuryl Oxalate, and Pentoxifylline; Sympathomimetics selected from the group consisting of Dopamine, Dopexamine, Ephedrine, Metaraminol, Noradrenaline Acid Tartrate, Norephidrine Bitartrate, and Phenylephidrine; Anticoagulants and protamine selected from the group consisting of Heparin, Bemiparin, Dalteparin, Enoxaparin, Tinzaparin, Danaparoid, Bivalirudin, Lepirudin, Epoprostenol, Fondaparinux, Warfarin, Acenocoumarol, Phenindione, Dabigatran Etexilate, Rivaroxaban, and Protamine Sulphate; Antiplatelet drugs selected from the group consisting of Abciximab, Aspirin, Clopidogrel, Dipyridamole, Eptifibatide, Prasugrel, and Tirofiban; Fibrinolytic and antifibrinolytic drugs selected from the group consisting of Alteplase, Reteplase, Streptokinase, Tenecteplase, Urokinase, Etaisylate, and Tranexamic Acid; Lipid regulating drugs selected from the group consisting of Atorvastatin, Fluvastatin, Pravastatin, Rosuvastatin, Simvastatin, Colesevam,

Colestyramine, Colestipol, Ezetimibe, Bezafibrate, Ciprofibrate, Fenofibrate, Gemfibrozyl, Acipmox, Nicotinic Acid, Omega three fatty acid compounds, Ethanolamine Oleate, and Sodium Tetradecyl Sulfate; CNS Drugs selected from the group consisting of Benperidol, Chlorpromazine, Flupentixol, Haloperidol, Levomepromazine, Pericyazine, Perphenazine, Pimozide, Prochlorperazine, Promazine, Sulpiride, Trifluoperazine, Zuclopenthixol, Amisulpride, Aripiprazole, Clozapine, Olanzapine, Paliperidone, Quetiapine, Risperidone, Sertindole, Zotepine, Flupentixol, Fluphenazine, Olanzapine Embonate, Pipotiazine Palmitate, Risperidone, Zuclopenthixol Decanoate, Carbamazepine, Valproate, Valproic acid, Lithium Carbonate, Lithium Citrate, Amitriptyline, Clomipramine, Dosulepin, Imipramine, Lofepramine, Nortriptyline, Trimipramine, mianserin, Trazodone, Phenelzine, Isocarboxazid, Tranlycypromine, Moclobemide, Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Agomelatine, Duloxetine, Flupentixol, Mirtazapine, Reboxetine, Tryptophan, Venflaxine, Atomoxetine, Dexametamine, Methylphenidate, Modafinil, Eslicarbazepine, Ocarbazepene, Ethosuximide, Gabapentin, Pregabalin, Lacosamide, Lamotrigine, Levetiracetam, Phenobarbital, Primidone, Phenytoin, Rufinamide, Tiagabine, Topiramate, Vigabatrin, Zonisamide, ropinirole, Rotigotine, Co-Beneldopa, Levodopa, Co-Careldopa, Rasagiline, Selegiline, Entacapone, Tolcapone, Amantidine, Orphenadrine, Procyclidine, Trihexyphenidyl, Haloperidol, Piracetam, Riluzole, Tetrabenazine, Acamprosate, Disulfiram, Bupropion, Vareniciline, Buprenorphine, Lofexidine, Donepezil, Galantamine, Memantine, and Rivastigimine; Anti-Infectives selected from the group consisting of Benzylpenicillin, Phenoxymethylpenicillin, Flucloxacillin, Temocillin, Amoxicillin, Ampicillin, Co-Amoxiclav, Co-Fluampicil, Piperacillin, Ticarcillin, Pivmecillinam, Cephalosporins, Cefaclor, Cefadroxil, Cefalexin, Cefixime, Cefotaxime, Cefradine, Ceftazidime, Cefuroxime, Ertapenem, Imipenem, Meropenem, Aztreonam, Tetracycline, Demeclocycline, Doxocycline, Lymecycline, Minocycline, Oxytetracycline, Tigecycline, Gentamicin, Amikacin, Neomycin, Tobramycin, Erythromycin, Azithromycin, Clarithromycin, Telithromycin, Clindamycin, Chloramphenicol, Fusidic Acid, Vancomycin, Teicoplanin, Daptomycin, Linezolid, Quinupristin, Colistin, Co-Trimoxazole, Sulpadiazine, Trimethoprim, Capreomycin, Cycloserine, Ethambutol, Isoniazid, Pyrazinamide, Rifabutin, Rifampicin, Streptomycin, Dapsone, Clofazimine, Metronidazole, Tinidazole, Ciprofloxacin, Levofloxacin, Moxifloxacin, Nalidixic Acid, Norflaxine, Ofloxacin, Nitrofurantoin, Methenamine Hippurate, Amphotericin, Anidulafungin, Caspofungin, Fluconazole, Flucytosine,

Griseofluvin, Itraconazole, Ketoconazole, Micafungin, Nystatin, Posaconazole, Terbinafine, Voriconazole, Abacavir, Didanosine, Emtricitabine, Lamivudine, Stavudine, Tenofovir Disoproxil, Zidovudine, Atazanavir, Darunavir, Fosamprenavir, Indinavir, Lopinair, Nelfinavir, Ritonavir, Saquinavir, Tipranavir, Efavirenz, Etravirine, Nevarapine, Enfuvirtide, Maraviroc, Raltegravir, Aciclovir, Famciclovir, Inosine Pranobex, Valaciclovir, Cidofovir, Gangciclovir, Foscarnet, Valganciclovir, Adefovir Dipivoxil, Entecavir, Telbivudine, Amantadine, Oseltamivir, Zanamivir, Palivizumab, Ribavirin, Artemether, Chloroquine, Mefloquine, Primaquine, Proguanil, Pyrimethamine, Quinine, Doxycyclin, Diloxanide Furoate, Metronidazole, Tinidazole, Mepacrine, Sodium Stibogluconate, Atovaquone, Pentamidine Isetionate, Mebendazole, and Piperazine; and other drugs selected from the group consisting of Benzotropine, procyclidine, biperiden, Amantadine, Bromocriptine, Pergolide, Entacapone, Tolcapone, Selegeline, Pramipexole, budesonide, formoterol, quetiapine fumarate, olanzapine, pioglitazone, montelukast, Zoledromic Acid, valsartan, latanoprost, Irbesartan, Clopidogrel, Atomoxetine, Dexamfetamine, Methylphenidate, Modafinil, Bleomycin, Dactinomycin, Daunorubicin, Idarubicin, Mitomycin, Mitoxantrone, Azacitidine, Capecitabine, Cladribine, Clofarabine, Cytarabine, Fludarabine, Flurouracil, Gemcitabine, mercaptopurine, methotrexate, Nelarabine, Pemetrexed, Raltitrexed, Thioguanine, Apomorphine, Betamethasone, Cortisone, Deflazacort, Dexamethasone, Hydrocortisone, Methylprednisolone, Prednisolone, Triamcinolone, Ciclosporine, Sirolimus, Tacrolimus, Interferon Alpha, and Interferon Beta.

[1695] Additional pharmaceutical agents that contain a vitamin and/or mineral supplement that can be prepared in a solid dosage form described herein include one or more of the following a vitamin and/or mineral supplements: Vitamin A, Biotin, Vitamin B1 (Thiamin), Vitamin B12, Vitamin B6, Calcium, Choline, Chromium, Copper, Vitamin C, Vitamin D (e.g., Vitamin D3), Vitamin E, Fluoride, Folate, Iodine, Iron, Vitamin K, Magnesium, Manganese, Niacin, Pantothenic Acid, Phosphorus, Potassium, Riboflavin, Selenium, Thiamin, and/or Zinc.

[1696] Additional pharmaceutical agents that contain a dietary supplement (e.g., a vitamin, a mineral, an herb, an amino acid, an oil, and/or an enzyme) that can be prepared in a solid dosage form described herein include one or more of the following dietary supplements: acacia rigidula, BMPEA, DMAA, DMBA, DMHA, methylsynephrine, phenibut, picamilon, caffeine, tianeptine, vinpocetine, fish oil, flaxseed oil, omega-3,

omega-6, omega-9, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and/or alpha-linolenic acid (ALA).

[1697] The dose of the additional pharmaceutical agent in the solid dosage form (e.g., wherein the dose is per capsule or tablet or total per total number of minitabets used in a capsule) can be a dose described herein for a pharmaceutical agent that comprises bacteria and/or mEVs.

[1698] The dose of the additional pharmaceutical agent in the solid dosage form (e.g., wherein the dose is per capsule or tablet or total per total number of minitabets used in a capsule) can be, e.g., about 0.001 mg to about 10 mg fixed dose (e.g., about 0.05 mg to about 10 mg; about 0.1 mg to about 10 mg; about 0.1 mg to about 5 mg; about 0.5 mg to about 5 mg; about 1mg, about 2mg, about 3mg, about 4mg, or about 5 mg).

[1699] The dose of the additional pharmaceutical agent in the solid dosage form (e.g., wherein the dose is per capsule or tablet or total per total number of minitabets used in a capsule) can be, particularly for a supplement, e.g., about 1 mg to about 2000 mg (e.g., about 25 mg; about 50 mg; about 100 mg; about 250 mg; about 500 mg; about 750 mg; about 1000 mg; about 1500 mg; or about 2000 mg) or about 10 IU to about 5000 IU (international units) (e.g., about 25 IU; about 50 IU; about 100 IU; about 250 IU; about 500 IU; about 750 IU; about 1000 IU; about 1500 IU; about 2000 IU; about 3000 IU; about 4000 IU; or about 5000 IU).

Additional Pharmaceutical agents for Combination Use

[1700] In certain aspects, the methods provided herein include the administration to a subject of a solid dosage form described herein either alone or in combination with an additional pharmaceutical agent. In some embodiments, the additional pharmaceutical agent is an immunosuppressant, an anti-inflammatory agent, a steroid, and/or a cancer therapeutic.

[1701] In some embodiments, the solid dosage form is administered to the subject before the additional pharmaceutical agent is administered (e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 hours before or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 days before). In some embodiments, the solid dosage form is administered to the subject after the additional pharmaceutical agent is administered (e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 hours after or at least 1, 2, 3, 4,

5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 days after). In some embodiments, the solid dosage form and the additional pharmaceutical agent are administered to the subject simultaneously or nearly simultaneously (e.g., administrations occur within an hour of each other).

[1702] In some embodiments, an antibiotic is administered to the subject before the solid dosage form is administered to the subject (e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 hours before or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 days before). In some embodiments, an antibiotic is administered to the subject after the solid dosage form is administered to the subject (e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 hours before or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 days after). In some embodiments, the solid dosage form and the antibiotic are administered to the subject simultaneously or nearly simultaneously (e.g., administrations occur within an hour of each other).

[1703] In some embodiments, the additional pharmaceutical agent is a cancer therapeutic. In some embodiments, the cancer therapeutic is a chemotherapeutic agent. Examples of such chemotherapeutic agents include, but are not limited to, alkylating agents such as thiotepa and cyclophosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphoramide and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin gammall and calicheamicin omegall; dynemicin, including dynemicin A; bisphosphonates, such as

clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores, aclacinomysins, actinomycin, authrarnycin, azaserine, bleomycins, cactinomycin, carabacin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitostanol, mepitostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK polysaccharide complex); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g., paclitaxel and doxetaxel; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum coordination complexes such as cisplatin, oxaliplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; irinotecan (e.g., CPT-11); topoisomerase inhibitor RFS 2000; difluoromethylomithine (DMFO); retinoids such as retinoic acid; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

[1704] In some embodiments, the cancer therapeutic is a cancer immunotherapy agent. Immunotherapy refers to a treatment that uses a subject's immune system to treat cancer, e.g., checkpoint inhibitors, cancer vaccines, cytokines, cell therapy, CAR-T cells, and dendritic cell therapy. Non-limiting examples of immunotherapies are checkpoint inhibitors include Nivolumab (BMS, anti-PD-1), Pembrolizumab (Merck, anti-PD-1), Ipilimumab (BMS, anti-CTLA-4), MEDI4736 (AstraZeneca, anti-PD-L1), and MPDL3280A (Roche, anti-PD-L1). Other immunotherapies may be tumor vaccines, such as Gardasil, Cervarix, BCG, sipulencel-T, Gp100:209-217, AGS-003, DCVax-L, Algenpantucel-L, Tergenpantucel-L, TG4010, ProstAtak, Prostavac-V/R-TRICOM, Rindopepimul, E75 peptide acetate, IMA901, POL-103A, Belagenpumatucel-L, GSK1572932A, MDX-1279, GV1001, and Tecemotide. The immunotherapy agent may be administered via injection (e.g., intravenously, intratumorally, subcutaneously, or into lymph nodes), but may also be administered orally, topically, or via aerosol. Immunotherapies may comprise adjuvants such as cytokines.

[1705] In some embodiments, the immunotherapy agent is an immune checkpoint inhibitor. Immune checkpoint inhibition broadly refers to inhibiting the checkpoints that cancer cells can produce to prevent or downregulate an immune response. Examples of immune checkpoint proteins include, but are not limited to, CTLA4, PD-1, PD-L1, PD-L2, A2AR, B7-H3, B7-H4, BTLA, KIR, LAG3, TIM-3 or VISTA. Immune checkpoint inhibitors can be antibodies or antigen binding fragments thereof that bind to and inhibit an immune checkpoint protein. Examples of immune checkpoint inhibitors include, but are not limited to, nivolumab, pembrolizumab, pidilizumab, AMP-224, AMP-514, STI-A1110, TSR-042, RG-7446, BMS-936559, MEDI-4736, MSB-0020718C, AUR-012 and STI-A1010.

[1706] In some embodiments, the methods provided herein include the administration of a pharmaceutical composition described herein in combination with one or more additional pharmaceutical agents. In some embodiments, the methods disclosed herein include the administration of two immunotherapy agents (e.g., immune checkpoint inhibitor). For example, the methods provided herein include the administration of a pharmaceutical composition described herein in combination with a PD-1 inhibitor (such as pemrolizumab or nivolumab or pidilizumab) or a CLTA-4 inhibitor (such as ipilimumab) or a PD-L1 inhibitor.

[1707] In some embodiments, the immunotherapy agent is an antibody or antigen binding fragment thereof that, for example, binds to a cancer-associated antigen. Examples of cancer-associated antigens include, but are not limited to, adipophilin, AIM-2, ALDH1A1, alpha-actinin-4, alpha-fetoprotein (“AFP”), ARTC1, B-RAF, BAGE-1, BCLX (L), BCR-ABL fusion protein b3a2, beta-catenin, BING-4, CA-125, CALCA, carcinoembryonic antigen (“CEA”), CASP-5, CASP-8, CD274, CD45, Cdc27, CDK12, CDK4, CDKN2A, CEA, CLPP, COA-1, CPSF, CSNK1A1, CTAG1, CTAG2, cyclin D1, Cyclin-A1, dek-can fusion protein, DKK1, EFTUD2, Elongation factor 2, ENAH (hMena), Ep-CAM, EpCAM, EphA3, epithelial tumor antigen (“ETA”), ETV6-AML1 fusion protein, EZH2, FGF5, FLT3-ITD, FN1, G250/MN/CAIX, GAGE-1,2,8, GAGE-3,4,5,6,7, GAS7, glypican-3, GnTV, gp100/Pmel17, GPNMB, HAUS3, Hepsin, HER-2/neu, HERV-K-MEL, HLA-A11, HLA-A2, HLA-DOB, hsp70-2, IDO1, IGF2B3, IL13Ralpha2, Intestinal carboxyl esterase, K-ras, Kallikrein 4, KIF20A, KK-LC-1, KKLC1, KM-HN-1, KMHN1 also known as CCDC110, LAGE-1, LDLR-fucosyltransferaseAS fusion protein, Lengsin, M-CSF, MAGE-A1, MAGE-A10, MAGE-A12, MAGE-A2, MAGE-A3, MAGE-A4, MAGE-A6, MAGE-A9, MAGE-C1, MAGE-C2, malic enzyme, mammaglobin-A, MART2, MATN, MC1R, MCSP, mdm-2, ME1, Melan-A/MART-1, Meloe, Midkine, MMP-2, MMP-7, MUC1, MUC5AC, mucin, MUM-1, MUM-2, MUM-3, Myosin, Myosin class I, N-ras, NA88-A, neo-PAP, NFYC, NY-BR-1, NY-ESO-1/LAGE-2, OA1, OGT, OS-9, P polypeptide, p53, PAP, PAX5, PBF, pml-RARalpha fusion protein, polymorphic epithelial mucin (“PEM”), PPP1R3B, PRAME, PRDX5, PSA, PSMA, PTPRK, RAB38/NY-MEL-1, RAGE-1, RBAF600, RGS5, RhoC, RNF43, RU2AS, SAGE, secernin 1, SIRT2, SNRPD1, SOX10, Sp17, SPA17, SSX-2, SSX-4, STEAP1, survivin, SYT-SSX1 or -SSX2 fusion protein, TAG-1, TAG-2, Telomerase, TGF-betaRII, TPBG, TRAG-3, Triosephosphate isomerase, TRP-1/gp75, TRP-2, TRP2-INT2, tyrosinase, tyrosinase (“TYR”), VEGF, WT1, XAGE-1b/GAGED2a. In some embodiments, the antigen is a neo-antigen.

[1708] In some embodiments, the immunotherapy agent is a cancer vaccine and/or a component of a cancer vaccine (e.g., an antigenic peptide and/or protein). The cancer vaccine can be a protein vaccine, a nucleic acid vaccine or a combination thereof. For example, in some embodiments, the cancer vaccine comprises a polypeptide comprising an epitope of a cancer-associated antigen. In some embodiments, the cancer vaccine comprises a nucleic acid (e.g., DNA or RNA, such as mRNA) that encodes an epitope of a cancer-

associated antigen. Examples of cancer-associated antigens include, but are not limited to, adipophilin, AIM-2, ALDH1A1, alpha-actinin-4, alpha-fetoprotein (“AFP”), ARTC1, B-RAF, BAGE-1, BCLX (L), BCR-ABL fusion protein b3a2, beta-catenin, BING-4, CA-125, CALCA, carcinoembryonic antigen (“CEA”), CASP-5, CASP-8, CD274, CD45, Cdc27, CDK12, CDK4, CDKN2A, CEA, CLPP, COA-1, CPSF, CSNK1A1, CTAG1, CTAG2, cyclin D1, Cyclin-A1, dek-can fusion protein, DKK1, EFTUD2, Elongation factor 2, ENAH (hMena), Ep-CAM, EpCAM, EphA3, epithelial tumor antigen (“ETA”), ETV6-AML1 fusion protein, EZH2, FGF5, FLT3-ITD, FN1, G250/MN/CAIX, GAGE-1,2,8, GAGE-3,4,5,6,7, GAS7, glypican-3, GnTV, gp100/Pmel17, GPNMB, HAUS3, Hepsin, HER-2/neu, HERV-K-MEL, HLA-A11, HLA-A2, HLA-DOB, hsp70-2, IDO1, IGF2B3, IL13Ralpha2, Intestinal carboxyl esterase, K-ras, Kallikrein 4, KIF20A, KK-LC-1, KKLC1, KM-HN-1, KMHN1 also known as CCDC110, LAGE-1, LDLR-fucosyltransferaseAS fusion protein, Lengsin, M-CSF, MAGE-A1, MAGE-A10, MAGE-A12, MAGE-A2, MAGE-A3, MAGE-A4, MAGE-A6, MAGE-A9, MAGE-C1, MAGE-C2, malic enzyme, mammaglobin-A, MART2, MATN, MC1R, MCSP, mdm-2, ME1, Melan-A/MART-1, Meloe, Midkine, MMP-2, MMP-7, MUC1, MUC5AC, mucin, MUM-1, MUM-2, MUM-3, Myosin, Myosin class I, N-ras, NA88-A, neo-PAP, NFYC, NY-BR-1, NY-ESO-1/LAGE-2, OA1, OGT, OS-9, P polypeptide, p53, PAP, PAX5, PBF, pml-RARalpha fusion protein, polymorphic epithelial mucin (“PEM”), PPP1R3B, PRAME, PRDX5, PSA, PSMA, PTPRK, RAB38/NY-MEL-1, RAGE-1, RBAF600, RGS5, RhoC, RNF43, RU2AS, SAGE, secernin 1, SIRT2, SNRPD1, SOX10, Sp17, SPA17, SSX-2, SSX-4, STEAP1, survivin, SYT-SSX1 or -SSX2 fusion protein, TAG-1, TAG-2, Telomerase, TGF-betaRII, TPBG, TRAG-3, Triosephosphate isomerase, TRP-1/gp75, TRP-2, TRP2-INT2, tyrosinase, tyrosinase (“TYR”), VEGF, WT1, XAGE-1b/GAGED2a. In some embodiments, the antigen is a neo-antigen. In some embodiments, the cancer vaccine is administered with an adjuvant. Examples of adjuvants include, but are not limited to, an immune modulatory protein, Adjuvant 65, α -GalCer, aluminum phosphate, aluminum hydroxide, calcium phosphate, β -Glucan Peptide, CpG ODN DNA, GPI-0100, lipid A, lipopolysaccharide, Lipovant, Montanide, N-acetyl-muramyl-L-alanyl-D-isoglutamine, Pam3CSK4, quil A, cholera toxin (CT) and heat-labile toxin from enterotoxigenic *Escherichia coli* (LT) including derivatives of these (CTB, mmCT, CTA1-DD, LTB, LTK63, LTR72, dmLT) and trehalose dimycolate.

[1709] In some embodiments, the immunotherapy agent is an immune modulating protein to the subject. In some embodiments, the immune modulatory protein is a cytokine or chemokine. Examples of immune modulating proteins include, but are not limited to, B lymphocyte chemoattractant ("BLC"), C-C motif chemokine 11 ("Eotaxin-1"), Eosinophil chemotactic protein 2 ("Eotaxin-2"), Granulocyte colony-stimulating factor ("G-CSF"), Granulocyte macrophage colony-stimulating factor ("GM-CSF"), 1-309, Intercellular Adhesion Molecule 1 ("ICAM-1"), Interferon alpha ("IFN-alpha"), Interferon beta ("IFN-beta"), Interferon gamma ("IFN-gamma"), Interleukin-1 alpha ("IL-1 alpha"), Interleukin-1 beta ("IL-1 beta"), Interleukin 1 receptor antagonist ("IL-1 ra"), Interleukin-2 ("IL-2"), Interleukin-4 ("IL-4"), Interleukin-5 ("IL-5"), Interleukin-6 ("IL-6"), Interleukin-6 soluble receptor ("IL-6 sR"), Interleukin-7 ("IL-7"), Interleukin-8 ("IL-8"), Interleukin-10 ("IL-10"), Interleukin-11 ("IL-11"), Subunit beta of Interleukin-12 ("IL-12 p40" or "IL-12 p70"), Interleukin-13 ("IL-13"), Interleukin-15 ("IL-15"), Interleukin-16 ("IL-16"), Interleukin-17A-F ("IL-17A-F"), Interleukin-18 ("IL-18"), Interleukin-21 ("IL-21"), Interleukin-22 ("IL-22"), Interleukin-23 ("IL-23"), Interleukin-33 ("IL-33"), Chemokine (C-C motif) Ligand 2 ("MCP-1"), Macrophage colony-stimulating factor ("M-CSF"), Monokine induced by gamma interferon ("MIG"), Chemokine (C-C motif) ligand 2 ("MIP-1 alpha"), Chemokine (C-C motif) ligand 4 ("MIP-1 beta"), Macrophage inflammatory protein-1-delta ("MIP-1 delta"), Platelet-derived growth factor subunit B ("PDGF-BB"), Chemokine (C-C motif) ligand 5, Regulated on Activation, Normal T cell Expressed and Secreted ("RANTES"), TIMP metalloproteinase inhibitor 1 ("TIMP-1"), TIMP metalloproteinase inhibitor 2 ("TIMP-2"), Tumor necrosis factor, lymphotoxin-alpha ("TNF alpha"), Tumor necrosis factor, lymphotoxin-beta ("TNF beta"), Soluble TNF receptor type 1 ("sTNFR1"), sTNFR2, Brain-derived neurotrophic factor ("BDNF"), Basic fibroblast growth factor ("bFGF"), Bone morphogenetic protein 4 ("BMP-4"), Bone morphogenetic protein 5 ("BMP-5"), Bone morphogenetic protein 7 ("BMP-7"), Nerve growth factor ("b-NGF"), Epidermal growth factor ("EGF"), Epidermal growth factor receptor ("EGFR"), Endocrine-gland-derived vascular endothelial growth factor ("EG-VEGF"), Fibroblast growth factor 4 ("FGF-4"), Keratinocyte growth factor ("FGF-7"), Growth differentiation factor 15 ("GDF-15"), Glial cell-derived neurotrophic factor ("GDNF"), Growth Hormone, Heparin-binding EGF-like growth factor ("HB-EGF"), Hepatocyte growth factor ("HGF"), Insulin-like growth factor binding protein 1 ("IGFBP-1"), Insulin-like growth factor binding protein 2 ("IGFBP-2"), Insulin-like growth factor binding protein 3 ("IGFBP-3"), Insulin-

like growth factor binding protein 4 ("IGFBP-4"), Insulin-like growth factor binding protein 6 ("IGFBP-6"), Insulin-like growth factor 1 ("IGF-1"), Insulin, Macrophage colony-stimulating factor ("M-CSF R"), Nerve growth factor receptor ("NGF R"), Neurotrophin-3 ("NT-3"), Neurotrophin-4 ("NT-4"), Osteoclastogenesis inhibitory factor ("Osteoprotegerin"), Platelet-derived growth factor receptors ("PDGF-AA"), Phosphatidylinositol-glycan biosynthesis ("PIGF"), Skp, Cullin, F-box containing complexes ("SCF"), Stem cell factor receptor ("SCF R"), Transforming growth factor alpha ("TGFalpha"), Transforming growth factor beta-1 ("TGF beta 1"), Transforming growth factor beta-3 ("TGF beta 3"), Vascular endothelial growth factor ("VEGF"), Vascular endothelial growth factor receptor 2 ("VEGFR2"), Vascular endothelial growth factor receptor 3 ("VEGFR3"), VEGF-D 6Ckine, Tyrosine-protein kinase receptor UFO ("Axl"), Betacellulin ("BTC"), Mucosae-associated epithelial chemokine ("CCL28"), Chemokine (C-C motif) ligand 27 ("CTACK"), Chemokine (C-X-C motif) ligand 16 ("CXCL16"), C-X-C motif chemokine 5 ("ENA-78"), Chemokine (C-C motif) ligand 26 ("Eotaxin-3"), Granulocyte chemotactic protein 2 ("GCP-2"), GRO, Chemokine (C-C motif) ligand 14 ("HCC-1"), Chemokine (C-C motif) ligand 16 ("HCC-4"), Interleukin-9 ("IL-9"), Interleukin-17 F ("IL-17F"), Interleukin-18-binding protein ("IL-18 BP α "), Interleukin-28 A ("IL-28A"), Interleukin 29 ("IL-29"), Interleukin 31 ("IL-31"), C-X-C motif chemokine 10 ("IP-10"), Chemokine receptor CXCR3 ("I-TAC"), Leukemia inhibitory factor ("LIF"), Light, Chemokine (C motif) ligand ("Lymphotactin"), Monocyte chemoattractant protein 2 ("MCP-2"), Monocyte chemoattractant protein 3 ("MCP-3"), Monocyte chemoattractant protein 4 ("MCP-4"), Macrophage-derived chemokine ("MDC"), Macrophage migration inhibitory factor ("MIF"), Chemokine (C-C motif) ligand 20 ("MIP-3 α "), C-C motif chemokine 19 ("MIP-3 β "), Chemokine (C-C motif) ligand 23 ("MPIF-1"), Macrophage stimulating protein alpha chain ("MSP α "), Nucleosome assembly protein 1-like 4 ("NAP-2"), Secreted phosphoprotein 1 ("Osteopontin"), Pulmonary and activation-regulated cytokine ("PARC"), Platelet factor 4 ("PF4"), Stroma cell-derived factor-1 α ("SDF-1 α "), Chemokine (C-C motif) ligand 17 ("TARC"), Thymus-expressed chemokine ("TECK"), Thymic stromal lymphopoietin ("TSLP 4-IBB"), CD 166 antigen ("ALCAM"), Cluster of Differentiation 80 ("B7-1"), Tumor necrosis factor receptor superfamily member 17 ("BCMA"), Cluster of Differentiation 14 ("CD14"), Cluster of Differentiation 30 ("CD30"), Cluster of Differentiation 40 ("CD40 Ligand"), Carcinoembryonic antigen-related cell adhesion molecule 1 (biliary glycoprotein)

("CEACAM-1"), Death Receptor 6 ("DR6"), Deoxythymidine kinase ("Dtk"), Type 1 membrane glycoprotein ("Endoglin"), Receptor tyrosine-protein kinase erbB-3 ("ErbB3"), Endothelial-leukocyte adhesion molecule 1 ("E-Selectin"), Apoptosis antigen 1 ("Fas"), Fms-like tyrosine kinase 3 ("Flt-3L"), Tumor necrosis factor receptor superfamily member 1 ("GITR"), Tumor necrosis factor receptor superfamily member 14 ("HVEM"), Intercellular adhesion molecule 3 ("ICAM-3"), IL-1 R4, IL-1 RI, IL-10 Rbeta, IL-17R, IL-2Rgamma, IL-21R, Lysosome membrane protein 2 ("LIMPII"), Neutrophil gelatinase-associated lipocalin ("Lipocalin-2"), CD62L ("L-Selectin"), Lymphatic endothelium ("LYVE-1"), MHC class I polypeptide-related sequence A ("MICA"), MHC class I polypeptide-related sequence B ("MICB"), NRG1-beta1, Beta-type platelet-derived growth factor receptor ("PDGF Rbeta"), Platelet endothelial cell adhesion molecule ("PECAM-1"), RAGE, Hepatitis A virus cellular receptor 1 ("TIM-1"), Tumor necrosis factor receptor superfamily member 10C ("TRAIL R3"), Trappin protein transglutaminase binding domain ("Trappin-2"), Urokinase receptor ("uPAR"), Vascular cell adhesion protein 1 ("VCAM-1"), XEDARActivin A, Agouti-related protein ("AgRP"), Ribonuclease 5 ("Angiogenin"), Angiopoietin 1, Angiostatin, Cathepsin S, CD40, Cryptic family protein IB ("Cripto-1"), DAN, Dickkopf-related protein 1 ("DKK-1"), E-Cadherin, Epithelial cell adhesion molecule ("EpCAM"), Fas Ligand (FasL or CD95L), Fcγ RIIB/C, FcγRIIb, Galectin-7, Intercellular adhesion molecule 2 ("ICAM-2"), IL-13 R1, IL-13R2, IL-17B, IL-2 Ra, IL-2 Rb, IL-23, LAP, Neuronal cell adhesion molecule ("NrCAM"), Plasminogen activator inhibitor-1 ("PAI-1"), Platelet derived growth factor receptors ("PDGF-AB"), Resistin, stromal cell-derived factor 1 ("SDF-1 beta"), sgp130, Secreted frizzled-related protein 2 ("ShhN"), Sialic acid-binding immunoglobulin-type lectins ("Siglec-5"), ST2, Transforming growth factor-beta 2 ("TGF beta 2"), Tie-2, Thrombopoietin ("TPO"), Tumor necrosis factor receptor superfamily member 10D ("TRAIL R4"), Triggering receptor expressed on myeloid cells 1 ("TREM-1"), Vascular endothelial growth factor C ("VEGF-C"), VEGFR1Adiponectin, Adipsin ("AND"), Alpha-fetoprotein ("AFP"), Angiopoietin-like 4 ("ANGPTL4"), Beta-2-microglobulin ("B2M"), Basal cell adhesion molecule ("BCAM"), Carbohydrate antigen 125 ("CA125"), Cancer Antigen 15-3 ("CA15-3"), Carcinoembryonic antigen ("CEA"), cAMP receptor protein ("CRP"), Human Epidermal Growth Factor Receptor 2 ("ErbB2"), Follistatin, Follicle-stimulating hormone ("FSH"), Chemokine (C-X-C motif) ligand 1 ("GRO alpha"), human chorionic gonadotropin ("beta HCG"), Insulin-like growth factor 1 receptor ("IGF-1 sR"), IL-1 sRII, IL-3, IL-18 Rb, IL-21, Leptin, Matrix

metalloproteinase-1 ("MMP-1"), Matrix metalloproteinase-2 ("MMP-2"), Matrix metalloproteinase-3 ("MMP-3"), Matrix metalloproteinase-8 ("MMP-8"), Matrix metalloproteinase-9 ("MMP-9"), Matrix metalloproteinase-10 ("MMP-10"), Matrix metalloproteinase-13 ("MMP-13"), Neural Cell Adhesion Molecule ("NCAM-1"), Entactin ("Nidogen-1"), Neuron specific enolase ("NSE"), Oncostatin M ("OSM"), Procalcitonin, Prolactin, Prostate specific antigen ("PSA"), Sialic acid-binding Ig-like lectin 9 ("Siglec-9"), ADAM 17 endopeptidase ("TACE"), Thyroglobulin, Metalloproteinase inhibitor 4 ("TIMP-4"), TSH2B4, Disintegrin and metalloproteinase domain-containing protein 9 ("ADAM-9"), Angiopoietin 2, Tumor necrosis factor ligand superfamily member 13/ Acidic leucine-rich nuclear phosphoprotein 32 family member B ("APRIL"), Bone morphogenetic protein 2 ("BMP-2"), Bone morphogenetic protein 9 ("BMP-9"), Complement component 5a ("C5a"), Cathepsin L, CD200, CD97, Chemerin, Tumor necrosis factor receptor superfamily member 6B ("DcR3"), Fatty acid-binding protein 2 ("FABP2"), Fibroblast activation protein, alpha ("FAP"), Fibroblast growth factor 19 ("FGF-19"), Galectin-3, Hepatocyte growth factor receptor ("HGF R"), IFN-gamma/alpha/beta R2, Insulin-like growth factor 2 ("IGF-2"), Insulin-like growth factor 2 receptor ("IGF-2 R"), Interleukin-1 receptor 6 ("IL-1R6"), Interleukin 24 ("IL-24"), Interleukin 33 ("IL-33"), Kallikrein 14, Asparaginyl endopeptidase ("Legumain"), Oxidized low-density lipoprotein receptor 1 ("LOX-1"), Mannose-binding lectin ("MBL"), Neprilysin ("NEP"), Notch homolog 1, translocation-associated (Drosophila) ("Notch-1"), Nephroblastoma overexpressed ("NOV"), Osteoactivin, Programmed cell death protein 1 ("PD-1"), N-acetylmuramoyl-L-alanine amidase ("PGRP-5"), Serpin A4, Secreted frizzled related protein 3 ("sFRP-3"), Thrombomodulin, Tolllike receptor 2 ("TLR2"), Tumor necrosis factor receptor superfamily member 10A ("TRAIL R1"), Transferrin ("TRF"), WIF-1/ACE-2, Albumin, AMICA, Angiopoietin 4, B-cell activating factor ("BAFF"), Carbohydrate antigen 19-9 ("CA19-9"), CD 163, Clusterin, CRT AM, Chemokine (C-X-C motif) ligand 14 ("CXCL14"), Cystatin C, Decorin ("DCN"), Dickkopf-related protein 3 ("Dkk-3"), Delta-like protein 1 ("DLL1"), Fetuin A, Heparin-binding growth factor 1 ("aFGF"), Folate receptor alpha ("FOLR1"), Furin, GPCR-associated sorting protein 1 ("GASP-1"), GPCR-associated sorting protein 2 ("GASP-2"), Granulocyte colony-stimulating factor receptor ("GCSF R"), Serine protease hepsin ("HAI-2"), Interleukin-17B Receptor ("IL-17B R"), Interleukin 27 ("IL-27"), Lymphocyte-activation gene 3 ("LAG-3"), Apolipoprotein A-V ("LDL R"), Pepsinogen I, Retinol binding protein 4 ("RBP4"),

SOST, Heparan sulfate proteoglycan ("Syndecan-1"), Tumor necrosis factor receptor superfamily member 13B ("TACI"), Tissue factor pathway inhibitor ("TFPI"), TSP-1, Tumor necrosis factor receptor superfamily, member 10b ("TRAIL R2"), TRANCE, Troponin I, Urokinase Plasminogen Activator ("uPA"), Cadherin 5, type 2 or VE-cadherin (vascular endothelial) also known as CD144 ("VE-Cadherin"), WNT1-inducible-signaling pathway protein 1 ("WISP-1"), and Receptor Activator of Nuclear Factor κ B ("RANK").

[1710] In some embodiments, the cancer therapeutic is an anti-cancer compound. Exemplary anti-cancer compounds include, but are not limited to, Alemtuzumab (Campath®), Alitretinoin (Panretin®), Anastrozole (Arimidex®), Bevacizumab (Avastin®), Bexarotene (Targretin®), Bortezomib (Velcade®), Bosutinib (Bosulif®), Brentuximab vedotin (Adcetris®), Cabozantinib (Cometriq™), Carfilzomib (Kyprolis™), Cetuximab (Erbix®), Crizotinib (Xalkori®), Dasatinib (Sprycel®), Denileukin diftitox (Ontak®), Erlotinib hydrochloride (Tarceva®), Everolimus (Afinitor®), Exemestane (Aromasin®), Fulvestrant (Faslodex®), Gefitinib (Iressa®), Ibritumomab tiuxetan (Zevalin®), Imatinib mesylate (Gleevec®), Ipilimumab (Yervoy™), Lapatinib ditosylate (Tykerb®), Letrozole (Femara®), Nilotinib (Tasigna®), Ofatumumab (Arzerra®), Panitumumab (Vectibix®), Pazopanib hydrochloride (Votrient®), Pertuzumab (Perjeta™), Pralatrexate (Folotyn®), Regorafenib (Stivarga®), Rituximab (Rituxan®), Romidepsin (Istodax®), Sorafenib tosylate (Nexavar®), Sunitinib malate (Sutent®), Tamoxifen, Temsirolimus (Torisel®), Toremifene (Fareston®), Tositumomab and ¹³¹I-tositumomab (Bexxar®), Trastuzumab (Herceptin®), Tretinoin (Vesanoid®), Vandetanib (Caprelsa®), Vemurafenib (Zelboraf®), Vorinostat (Zolinza®), and Ziv-aflibercept (Zaltrap®).

[1711] Exemplary anti-cancer compounds that modify the function of proteins that regulate gene expression and other cellular functions (e.g., HDAC inhibitors, retinoid receptor ligands) are Vorinostat (Zolinza®), Bexarotene (Targretin®) and Romidepsin (Istodax®), Alitretinoin (Panretin®), and Tretinoin (Vesanoid®).

[1712] Exemplary anti-cancer compounds that induce apoptosis (e.g., proteasome inhibitors, antifolates) are Bortezomib (Velcade®), Carfilzomib (Kyprolis™), and Pralatrexate (Folotyn®).

[1713] Exemplary anti-cancer compounds that increase anti-tumor immune response (e.g., anti CD20, anti CD52; anti-cytotoxic T-lymphocyte-associated antigen-4) are Rituximab (Rituxan®), Alemtuzumab (Campath®), Ofatumumab (Arzerra®), and Ipilimumab (Yervoy™).

[1714] Exemplary anti-cancer compounds that deliver toxic agents to cancer cells (e.g., anti-CD20-radionuclide fusions; IL-2-diphtheria toxin fusions; anti-CD30-monomethylauristatin E (MMAE)-fusions) are Tositumomab and ¹³¹I-tositumomab (Bexxar®) and Ibritumomab tiuxetan (Zevalin®), Denileukin diftitox (Ontak®), and Brentuximab vedotin (Adcetris®).

[1715] Other exemplary anti-cancer compounds are small molecule inhibitors and conjugates thereof of, e.g., Janus kinase, ALK, Bcl-2, PARP, PI3K, VEGF receptor, Braf, MEK, CDK, and HSP90.

[1716] Exemplary platinum-based anti-cancer compounds include, for example, cisplatin, carboplatin, oxaliplatin, satraplatin, picoplatin, Nedaplatin, Triplatin, and Lipoplatin. Other metal-based drugs suitable for treatment include, but are not limited to ruthenium-based compounds, ferrocene derivatives, titanium-based compounds, and gallium-based compounds.

[1717] In some embodiments, the cancer therapeutic is a radioactive moiety that comprises a radionuclide. Exemplary radionuclides include, but are not limited to Cr-51, Cs-131, Ce-134, Se-75, Ru-97, I-125, Eu-149, Os-189m, Sb-119, I-123, Ho-161, Sb-117, Ce-139, In-111, Rh-103m, Ga-67, Tl-201, Pd-103, Au-195, Hg-197, Sr-87m, Pt-191, P-33, Er-169, Ru-103, Yb-169, Au-199, Sn-121, Tm-167, Yb-175, In-113m, Sn-113, Lu-177, Rh-105, Sn-117m, Cu-67, Sc-47, Pt-195m, Ce-141, I-131, Tb-161, As-77, Pt-197, Sm-153, Gd-159, Tm-173, Pr-143, Au-198, Tm-170, Re-186, Ag-111, Pd-109, Ga-73, Dy-165, Pm-149, Sn-123, Sr-89, Ho-166, P-32, Re-188, Pr-142, Ir-194, In-114m/In-114, and Y-90.

[1718] In some embodiments, the cancer therapeutic is an antibiotic. For example, if the presence of a cancer-associated bacteria and/or a cancer-associated microbiome profile is detected according to the methods provided herein, antibiotics can be administered to eliminate the cancer-associated bacteria from the subject. “Antibiotics” broadly refers to compounds capable of inhibiting or preventing a bacterial infection. Antibiotics can be classified in a number of ways, including their use for specific infections, their mechanism of action, their bioavailability, or their spectrum of target microbe (e.g., Gram-negative vs. Gram-positive bacteria, aerobic vs. anaerobic bacteria, etc.) and these may be used to kill specific bacteria in specific areas of the host (“niches”) (Leekha, et al 2011. General Principles of Antimicrobial Therapy. Mayo Clin Proc. 86(2): 156-167). In certain embodiments, antibiotics can be used to selectively target bacteria of a specific niche. In some embodiments, antibiotics known to treat a particular infection that includes a cancer

niche may be used to target cancer-associated microbes, including cancer-associated bacteria in that niche. In other embodiments, antibiotics are administered after the solid dosage form. In some embodiments, antibiotics are administered before the solid dosage form.

[1719] In some aspects, antibiotics can be selected based on their bactericidal or bacteriostatic properties. Bactericidal antibiotics include mechanisms of action that disrupt the cell wall (e.g., β -lactams), the cell membrane (e.g., daptomycin), or bacterial DNA (e.g., fluoroquinolones). Bacteriostatic agents inhibit bacterial replication and include sulfonamides, tetracyclines, and macrolides, and act by inhibiting protein synthesis. Furthermore, while some drugs can be bactericidal in certain organisms and bacteriostatic in others, knowing the target organism allows one skilled in the art to select an antibiotic with the appropriate properties. In certain treatment conditions, bacteriostatic antibiotics inhibit the activity of bactericidal antibiotics. Thus, in certain embodiments, bactericidal and bacteriostatic antibiotics are not combined.

[1720] Antibiotics include, but are not limited to aminoglycosides, ansamycins, carbacephems, carbapenems, cephalosporins, glycopeptides, lincosamides, lipopeptides, macrolides, monobactams, nitrofurans, oxazolidinones, penicillins, polypeptide antibiotics, quinolones, fluoroquinolone, sulfonamides, tetracyclines, and anti-mycobacterial compounds, and combinations thereof.

[1721] Aminoglycosides include, but are not limited to Amikacin, Gentamicin, Kanamycin, Neomycin, Netilmicin, Tobramycin, Paromomycin, and Spectinomycin. Aminoglycosides are effective, e.g., against Gram-negative bacteria, such as *Escherichia coli*, *Klebsiella*, *Pseudomonas aeruginosa*, and *Francisella tularensis*, and against certain aerobic bacteria but less effective against obligate/facultative anaerobes. Aminoglycosides are believed to bind to the bacterial 30S or 50S ribosomal subunit thereby inhibiting bacterial protein synthesis.

[1722] Ansamycins include, but are not limited to, Geldanamycin, Herbimycin, Rifamycin, and Streptovaricin. Geldanamycin and Herbimycin are believed to inhibit or alter the function of Heat Shock Protein 90.

[1723] Carbacephems include, but are not limited to, Loracarbef. Carbacephems are believed to inhibit bacterial cell wall synthesis.

[1724] Carbapenems include, but are not limited to, Ertapenem, Doripenem, Imipenem/Cilastatin, and Meropenem. Carbapenems are bactericidal for both Gram-

positive and Gram-negative bacteria as broad-spectrum antibiotics. Carbapenems are believed to inhibit bacterial cell wall synthesis.

[1725] Cephalosporins include, but are not limited to, Cefadroxil, Cefazolin, Cefalotin, Cefalothin, Cefalexin, Cefaclor, Cefamandole, Cefoxitin, Cefprozil, Cefuroxime, Cefixime, Cefdinir, Cefditoren, Cefoperazone, Cefotaxime, Cefpodoxime, Ceftazidime, Ceftibuten, Ceftizoxime, Ceftriaxone, Cefepime, Ceftaroline fosamil, and Ceftobiprole. Selected Cephalosporins are effective, e.g., against Gram-negative bacteria and against Gram-positive bacteria, including *Pseudomonas*, certain Cephalosporins are effective against methicillin-resistant *Staphylococcus aureus* (MRSA). Cephalosporins are believed to inhibit bacterial cell wall synthesis by disrupting synthesis of the peptidoglycan layer of bacterial cell walls.

[1726] Glycopeptides include, but are not limited to, Teicoplanin, Vancomycin, and Telavancin. Glycopeptides are effective, e.g., against aerobic and anaerobic Gram-positive bacteria including MRSA and *Clostridium difficile*. Glycopeptides are believed to inhibit bacterial cell wall synthesis by disrupting synthesis of the peptidoglycan layer of bacterial cell walls.

[1727] Lincosamides include, but are not limited to, Clindamycin and Lincomycin. Lincosamides are effective, e.g., against anaerobic bacteria, as well as *Staphylococcus*, and *Streptococcus*. Lincosamides are believed to bind to the bacterial 50S ribosomal subunit thereby inhibiting bacterial protein synthesis.

[1728] Lipopeptides include, but are not limited to, Daptomycin. Lipopeptides are effective, e.g., against Gram-positive bacteria. Lipopeptides are believed to bind to the bacterial membrane and cause rapid depolarization.

[1729] Macrolides include, but are not limited to, Azithromycin, Clarithromycin, Dirithromycin, Erythromycin, Roxithromycin, Troleandomycin, Telithromycin, and Spiramycin. Macrolides are effective, e.g., against *Streptococcus* and *Mycoplasma*. Macrolides are believed to bind to the bacterial or 50S ribosomal subunit, thereby inhibiting bacterial protein synthesis.

[1730] Monobactams include, but are not limited to, Aztreonam. Monobactams are effective, e.g., against Gram-negative bacteria. Monobactams are believed to inhibit bacterial cell wall synthesis by disrupting synthesis of the peptidoglycan layer of bacterial cell walls.

[1731] Nitrofurans include, but are not limited to, Furazolidone and Nitrofurantoin.

[1732] Oxazolidonones include, but are not limited to, Linezolid, Posizolid, Radezolid, and Torezolid. Oxazolidonones are believed to be protein synthesis inhibitors.

[1733] Penicillins include, but are not limited to, Amoxicillin, Ampicillin, Azlocillin, Carbenicillin, Cloxacillin, Dicloxacillin, Flucloxacillin, Mezlocillin, Methicillin, Nafcillin, Oxacillin, Penicillin G, Penicillin V, Piperacillin, Temocillin and Ticarcillin. Penicillins are effective, e.g., against Gram-positive bacteria, facultative anaerobes, e.g., *Streptococcus*, *Borrelia*, and *Treponema*. Penicillins are believed to inhibit bacterial cell wall synthesis by disrupting synthesis of the peptidoglycan layer of bacterial cell walls.

[1734] Penicillin combinations include, but are not limited to, Amoxicillin/clavulanate, Ampicillin/sulbactam, Piperacillin/tazobactam, and Ticarcillin/clavulanate.

[1735] Polypeptide antibiotics include, but are not limited to, Bacitracin, Colistin, and Polymyxin B and E. Polypeptide Antibiotics are effective, e.g., against Gram-negative bacteria. Certain polypeptide antibiotics are believed to inhibit isoprenyl pyrophosphate involved in synthesis of the peptidoglycan layer of bacterial cell walls, while others destabilize the bacterial outer membrane by displacing bacterial counter-ions.

[1736] Quinolones and Fluoroquinolone include, but are not limited to, Ciprofloxacin, Enoxacin, Gatifloxacin, Gemifloxacin, Levofloxacin, Lomefloxacin, Moxifloxacin, Nalidixic acid, Norfloxacin, Ofloxacin, Trovafloxacin, Grepafloxacin, Sparfloxacin, and Temafloxacin. Quinolones/Fluoroquinolone are effective, e.g., against *Streptococcus* and *Neisseria*. Quinolones/Fluoroquinolone are believed to inhibit the bacterial DNA gyrase or topoisomerase IV, thereby inhibiting DNA replication and transcription.

[1737] Sulfonamides include, but are not limited to, Mafenide, Sulfacetamide, Sulfadiazine, Silver sulfadiazine, Sulfadimethoxine, Sulfamethizole, Sulfamethoxazole, Sulfanilimide, Sulfasalazine, Sulfisoxazole, Trimethoprim-Sulfamethoxazole (Co-trimoxazole), and Sulfonamidochrysoidine. Sulfonamides are believed to inhibit folate synthesis by competitive inhibition of dihydropteroate synthetase, thereby inhibiting nucleic acid synthesis.

[1738] Tetracyclines include, but are not limited to, Demeclocycline, Doxycycline, Minocycline, Oxytetracycline, and Tetracycline. Tetracyclines are effective, e.g., against Gram-negative bacteria. Tetracyclines are believed to bind to the bacterial 30S ribosomal subunit thereby inhibiting bacterial protein synthesis.

[1739] Anti-mycobacterial compounds include, but are not limited to, Clofazimine, Dapsone, Capreomycin, Cycloserine, Ethambutol, Ethionamide, Isoniazid, Pyrazinamide, Rifampicin, Rifabutin, Rifapentine, and Streptomycin.

[1740] Suitable antibiotics also include arspenamine, chloramphenicol, fosfomycin, fusidic acid, metronidazole, mupirocin, platensimycin, quinupristin/dalfopristin, tigecycline, tinidazole, trimethoprim amoxicillin/clavulanate, ampicillin/sulbactam, amphomycin ristocetin, azithromycin, bacitracin, buforin II, carbomycin, cecropin PI, clarithromycin, erythromycins, furazolidone, fusidic acid, Na fusidate, gramicidin, imipenem, indolicidin, josamycin, magainan II, metronidazole, nitroimidazoles, mikamycin, mutacin B-Ny266, mutacin B-JHI 140, mutacin J-T8, nisin, nisin A, novobiocin, oleandomycin, ostreogrycin, piperacillin/tazobactam, pristinamycin, ramoplanin, ranalexin, reuterin, rifaximin, rosamicin, rosaramicin, spectinomycin, spiramycin, staphylomycin, streptogramin, streptogramin A, synergistin, taurolidine, teicoplanin, telithromycin, ticarcillin/clavulanic acid, triacetyloleandomycin, tylosin, tyrocidin, tyrothricin, vancomycin, vemamycin, and virginiamycin.

[1741] In some embodiments, the additional pharmaceutical agent is an immunosuppressive agent, a DMARD, a pain-control drug, a steroid, a non-steroidal antiinflammatory drug (NSAID), or a cytokine antagonist, and combinations thereof. Representative agents include, but are not limited to, cyclosporin, retinoids, corticosteroids, propionic acid derivative, acetic acid derivative, enolic acid derivatives, fenamic acid derivatives, Cox-2 inhibitors, lumiracoxib, ibuprophen, cholin magnesium salicylate, fenoprofen, salsalate, difunisal, tolmetin, ketoprofen, flurbiprofen, oxaprozin, indomethacin, sulindac, etodolac, ketorolac, nabumetone, naproxen, valdecoxib, etoricoxib, MK0966; rofecoxib, acetaminophen, Celecoxib, Diclofenac, tramadol, piroxicam, meloxicam, tenoxicam, droxicam, lornoxicam, isoxicam, mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic, valdecoxib, parecoxib, etodolac, indomethacin, aspirin, ibuprophen, firocoxib, methotrexate (MTX), antimalarial drugs (e.g., hydroxychloroquine and chloroquine), sulfasalazine, Leflunomide, azathioprine, cyclosporin, gold salts, minocycline, cyclophosphamide, D-penicillamine, minocycline, auranofin, tacrolimus, myocrisin, chlorambucil, TNF alpha antagonists (e.g., TNF alpha antagonists or TNF alpha receptor antagonists), e.g., ADALIMUMAB (Humira®), ETANERCEPT (Enbrel®), INFLIXIMAB (Remicade®; TA-650), CERTOLIZUMAB PEGOL (Cimzia®; CDP870), GOLIMUMAB (Simpom®; CNTO 148), ANAKINRA (Kineret®), RITUXIMAB

(Rituxan®; MabThera®), ABATACEPT (Orencia®), TOCILIZUMAB (RoActemra /Actemra®), integrin antagonists (TYSABRI® (natalizumab)), IL-1 antagonists (ACZ885 (Ilaris)), Anakinra (Kineret®)), CD4 antagonists, IL-23 antagonists, IL-20 antagonists, IL-6 antagonists, BLYS antagonists (e.g., Atacicept, Benlysta®/ LymphoStat-B® (belimumab)), p38 Inhibitors, CD20 antagonists (Ocrelizumab, Ofatumumab (Arzerra®)), interferon gamma antagonists (Fontolizumab), prednisolone, Prednisone, dexamethasone, Cortisol, cortisone, hydrocortisone, methylprednisolone, betamethasone, triamcinolone, beclometasone, fludrocortisone, deoxycorticosterone, aldosterone, Doxycycline, vancomycin, pioglitazone, SBI-087, SCIO-469, Cura-100, Oncoxin + Viusid, TwHF, Methoxsalen, Vitamin D - ergocalciferol, Milnacipran, Paclitaxel, rosiglitazone, Tacrolimus (Prograf®), RADOOL, rapamune, rapamycin, fostamatinib, Fentanyl, XOMA 052, Fostamatinib disodium, rosiglitazone, Curcumin (Longvida™), Rosuvastatin, Maraviroc, ramipril, Milnacipran, Cobiprostone, somatropin, tgAAC94 gene therapy vector, MK0359, GW856553, esomeprazole, everolimus, trastuzumab, JAK1 and JAK2 inhibitors, pan JAK inhibitors, e.g., tetracyclic pyridone 6 (P6), 325, PF-956980, denosumab, IL-6 antagonists, CD20 antagonists, CTLA4 antagonists, IL-8 antagonists, IL-21 antagonists, IL-22 antagonist, integrin antagonists (Tysabri® (natalizumab)), VEGF antagonists, CXCL antagonists, MMP antagonists, defensin antagonists, IL-1 antagonists (including IL-1 beta antagonists), and IL-23 antagonists (e.g., receptor decoys, antagonistic antibodies, etc.).

[1742] In some embodiments, the additional pharmaceutical agent is 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, TLR antagonists, inflammasome inhibitors, 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 pegol, golimumab, or etanercept, and combinations thereof.

Administration

[1743] In certain aspects, provided herein is a method of delivering a solid dosage form described herein to a subject. In some embodiments of the methods provided herein, the solid dosage form is administered in conjunction with the administration of an additional pharmaceutical agent. In some embodiments, the solid dosage form comprises a pharmaceutical agent that comprises bacteria and/or mEVs co-formulated with the additional pharmaceutical agent. In some embodiments, the solid dosage form is co-administered with the additional pharmaceutical agent. In some embodiments, the additional pharmaceutical agent is administered to the subject before administration of the solid dosage form (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50 or 55 minutes before, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22 or 23 hours before, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 days before). In some embodiments, the additional pharmaceutical agent is administered to the subject after administration of the solid dosage form (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50 or 55 minutes after, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22 or 23 hours after, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 days after). In some embodiments, the same mode of delivery is used to deliver both the solid dosage form and the additional pharmaceutical agent. In some embodiments, different modes of delivery are used to administer the solid dosage form and the additional pharmaceutical agent. For example, in some embodiments the solid dosage form is administered orally while the additional pharmaceutical agent is administered via injection (e.g., an intravenous, intramuscular and/or intratumoral injection).

[1744] In certain embodiments, the solid dosage form described herein can be administered in conjunction with any other conventional anti-cancer treatment, such as, for example, radiation therapy and surgical resection of the tumor. These treatments may be applied as necessary and/or as indicated and may occur before, concurrent with or after administration of the solid dosage form described herein.

[1745] The dosage regimen can be any of a variety of methods and amounts, and can be determined by one skilled in the art according to known clinical factors. As is known in the medical arts, dosages for any one patient can depend on many factors, including the subject's species, size, body surface area, age, sex, immunocompetence, and general health, the particular microorganism to be administered, duration and route of administration, the kind and stage of the disease, for example, tumor size, and other compounds such as drugs

being administered concurrently or near-concurrently. In addition to the above factors, such levels can be affected by the infectivity of the microorganism, and the nature of the microorganism, as can be determined by one skilled in the art. In the present methods, appropriate minimum dosage levels of microorganisms can be levels sufficient for the microorganism to survive, grow and replicate. The dose of a pharmaceutical agent (e.g., in a solid dosage form) described herein may be appropriately set or adjusted in accordance with the dosage form, the route of administration, the degree or stage of a target disease, and the like. For example, the general effective dose of the agents may range between 0.01 mg/kg body weight/day and 1000 mg/kg body weight/day, between 0.1 mg/kg body weight/day and 1000 mg/kg body weight/day, 0.5 mg/kg body weight/day and 500 mg/kg body weight/day, 1 mg/kg body weight/day and 100 mg/kg body weight/day, or between 5 mg/kg body weight/day and 50 mg/kg body weight/day. The effective dose may be 0.01, 0.05, 0.1, 0.5, 1, 2, 3, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 500, or 1000 mg/kg body weight/day or more, but the dose is not limited thereto.

[1746] In some embodiments, the dose administered to a subject is sufficient to prevent disease (e.g., autoimmune disease, inflammatory disease, metabolic disease, dysbiosis, or cancer), delay its onset, or slow or stop its progression, or relieve one or more symptoms of the disease. One skilled in the art will recognize that dosage will depend upon a variety of factors including the strength of the particular agent (e.g., pharmaceutical agent) employed, as well as the age, species, condition, and body weight of the subject. The size of the dose will also be determined by the route, timing, and frequency of administration as well as the existence, nature, and extent of any adverse side-effects that might accompany the administration of a particular pharmaceutical agent and the desired physiological effect.

[1747] Suitable doses and dosage regimens can be determined by conventional range-finding techniques known to those of ordinary skill in the art. Generally, treatment is initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. An effective dosage and treatment protocol can be determined by routine and conventional means, starting e.g., with a low dose in laboratory animals and then increasing the dosage while monitoring the effects, and systematically varying the dosage regimen as well. Animal studies are commonly used to determine the maximal tolerable dose ("MTD") of bioactive agent per kilogram weight. Those skilled in the art

regularly extrapolate doses for efficacy, while avoiding toxicity, in other species, including humans.

[1748] In accordance with the above, in therapeutic applications, the dosages of the pharmaceutical agents used in accordance with the invention vary depending on the active agent, the age, weight, and clinical condition of the recipient patient, and the experience and judgment of the clinician or practitioner administering the therapy, among other factors affecting the selected dosage. For example, for cancer treatment, the dose should be sufficient to result in slowing, and preferably regressing, the growth of a tumor and most preferably causing complete regression of the cancer, or reduction in the size or number of metastases. As another example, the dose should be sufficient to result in slowing of progression of the disease for which the subject is being treated, and preferably amelioration of one or more symptoms of the disease for which the subject is being treated.

[1749] Separate administrations can include any number of two or more administrations, including two, three, four, five or six administrations. One skilled in the art can readily determine the number of administrations to perform or the desirability of performing one or more additional administrations according to methods known in the art for monitoring therapeutic methods and other monitoring methods provided herein. Accordingly, the methods provided herein include methods of providing to the subject one or more administrations of a solid dosage form, where the number of administrations can be determined by monitoring the subject, and, based on the results of the monitoring, determining whether or not to provide one or more additional administrations. Deciding on whether or not to provide one or more additional administrations can be based on a variety of monitoring results.

[1750] The time period between administrations can be any of a variety of time periods. The time period between administrations can be a function of any of a variety of factors, including monitoring steps, as described in relation to the number of administrations, the time period for a subject to mount an immune response. In one example, the time period can be a function of the time period for a subject to mount an immune response; for example, the time period can be more than the time period for a subject to mount an immune response, such as more than about one week, more than about ten days, more than about two weeks, or more than about a month; in another example, the time period can be less than the time period for a subject to mount an immune response,

such as less than about one week, less than about ten days, less than about two weeks, or less than about a month.

[1751] In some embodiments, the delivery of an additional pharmaceutical agent in combination with the solid dosage form described herein reduces the adverse effects and/or improves the efficacy of the additional pharmaceutical agent.

[1752] The effective dose of an additional pharmaceutical agent described herein is the amount of the additional pharmaceutical agent that is effective to achieve the desired therapeutic response for a particular subject, composition, and mode of administration, with the least toxicity to the subject. The effective dosage level can be identified using the methods described herein and will depend upon a variety of pharmacokinetic factors including the activity of the particular compositions or agents administered, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the subject being treated, and like factors well known in the medical arts. In general, an effective dose of an additional pharmaceutical agent will be the amount of the additional pharmaceutical agent which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above.

[1753] The toxicity of an additional pharmaceutical agent is the level of adverse effects experienced by the subject during and following treatment. Adverse events associated with additional therapy toxicity can include, but are not limited to, abdominal pain, acid indigestion, acid reflux, allergic reactions, alopecia, anaphylaxis, anemia, anxiety, lack of appetite, arthralgias, asthenia, ataxia, azotemia, loss of balance, bone pain, bleeding, blood clots, low blood pressure, elevated blood pressure, difficulty breathing, bronchitis, bruising, low white blood cell count, low red blood cell count, low platelet count, cardiotoxicity, cystitis, hemorrhagic cystitis, arrhythmias, heart valve disease, cardiomyopathy, coronary artery disease, cataracts, central neurotoxicity, cognitive impairment, confusion, conjunctivitis, constipation, coughing, cramping, cystitis, deep vein thrombosis, dehydration, depression, diarrhea, dizziness, dry mouth, dry skin, dyspepsia, dyspnea, edema, electrolyte imbalance, esophagitis, fatigue, loss of fertility, fever, flatulence, flushing, gastric reflux, gastroesophageal reflux disease, genital pain, granulocytopenia, gynecomastia, glaucoma, hair loss, hand-foot syndrome, headache,

hearing loss, heart failure, heart palpitations, heartburn, hematoma, hemorrhagic cystitis, hepatotoxicity, hyperamylasemia, hypercalcemia, hyperchloremia, hyperglycemia, hyperkalemia, hyperlipasemia, hypermagnesemia, hypernatremia, hyperphosphatemia, hyperpigmentation, hypertriglyceridemia, hyperuricemia, hypoalbuminemia, hypocalcemia, hypochloremia, hypoglycemia, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, impotence, infection, injection site reactions, insomnia, iron deficiency, itching, joint pain, kidney failure, leukopenia, liver dysfunction, memory loss, menopause, mouth sores, mucositis, muscle pain, myalgias, myelosuppression, myocarditis, neutropenic fever, nausea, nephrotoxicity, neutropenia, nosebleeds, numbness, ototoxicity, pain, palmar-plantar erythrodysesthesia, pancytopenia, pericarditis, peripheral neuropathy, pharyngitis, photophobia, photosensitivity, pneumonia, pneumonitis, proteinuria, pulmonary embolus, pulmonary fibrosis, pulmonary toxicity, rash, rapid heart beat, rectal bleeding, restlessness, rhinitis, seizures, shortness of breath, sinusitis, thrombocytopenia, tinnitus, urinary tract infection, vaginal bleeding, vaginal dryness, vertigo, water retention, weakness, weight loss, weight gain, and xerostomia. In general, toxicity is acceptable if the benefits to the subject achieved through the therapy outweigh the adverse events experienced by the subject due to the therapy.

Immune Disorders

[1754] In some embodiments, the methods and solid dosage forms described herein relate to the treatment or prevention of 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). In some embodiments, the disease or disorder is psoriasis. In some embodiments, the disease or disorder is atopic dermatitis.

[1755] The methods and solid dosage forms 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.

[1756] The solid dosage forms described herein can be used, for example, as a pharmaceutical composition for preventing or treating (reducing, partially or completely,

the adverse effects of) an autoimmune disease, such as chronic inflammatory bowel disease, systemic lupus erythematosus, psoriasis, muckle-wells syndrome, 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 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 immune cells.

[1757] In some embodiments, the methods and solid dosage forms provided herein are useful for the treatment of inflammation. In certain embodiments, the inflammation of any tissue and organs of the body, including musculoskeletal inflammation, vascular inflammation, neural inflammation, digestive system inflammation, ocular inflammation, inflammation of the reproductive system, and other inflammation, as discussed below.

[1758] Immune disorders of the musculoskeletal system include, but are not limited, to those conditions affecting skeletal joints, including joints of the hand, wrist, elbow, shoulder, jaw, spine, neck, hip, knee, ankle, and foot, and conditions affecting tissues connecting muscles to bones such as tendons. Examples of such immune disorders, which may be treated with the methods and compositions described herein include, but are not limited to, arthritis (including, for example, osteoarthritis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, acute and chronic infectious arthritis, arthritis associated with gout and pseudogout, and juvenile idiopathic arthritis), tendonitis, synovitis, tenosynovitis, bursitis, fibrositis (fibromyalgia), epicondylitis, myositis, and osteitis (including, for example, Paget's disease, osteitis pubis, and osteitis fibrosa cystica).

[1759] Ocular immune disorders refers to a immune disorder that affects any structure of the eye, including the eye lids. Examples of ocular immune disorders which may be treated with the methods and compositions described herein include, but are not limited to, blepharitis, blepharochalasis, conjunctivitis, dacryoadenitis, keratitis, keratoconjunctivitis sicca (dry eye), scleritis, trichiasis, and uveitis.

[1760] Examples of nervous system immune disorders which may be treated with the methods and solid dosage forms described herein include, but are not limited to,

encephalitis, Guillain-Barre syndrome, meningitis, neuromyotonia, narcolepsy, multiple sclerosis, myelitis and schizophrenia. Examples of inflammation of the vasculature or lymphatic system which may be treated with the methods and compositions described herein include, but are not limited to, arthrosclerosis, arthritis, phlebitis, vasculitis, and lymphangitis.

[1761] Examples of digestive system immune disorders which may be treated with the methods and solid dosage forms described herein include, but are not limited to, cholangitis, cholecystitis, enteritis, enterocolitis, gastritis, gastroenteritis, inflammatory bowel disease, ileitis, and proctitis. 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, 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.

[1762] Examples of reproductive system immune disorders which may be treated with the methods and solid dosage forms described herein include, but are not limited to, cervicitis, chorioamnionitis, endometritis, epididymitis, omphalitis, oophoritis, orchitis, salpingitis, tubo-ovarian abscess, urethritis, vaginitis, vulvitis, and vulvodynia.

[1763] The methods and solid dosage forms described herein may be used to treat autoimmune conditions having an inflammatory component. Such conditions include, but are not limited to, acute disseminated alopecia universalis, Behcet's disease, Chagas' disease, chronic fatigue syndrome, dysautonomia, encephalomyelitis, ankylosing spondylitis, aplastic anemia, hidradenitis suppurativa, autoimmune hepatitis, autoimmune oophoritis, celiac disease, Crohn's disease, diabetes mellitus type 1, giant cell arteritis, goodpasture's syndrome, Grave's disease, Guillain-Barre syndrome, Hashimoto's disease, Henoch-Schonlein purpura, Kawasaki's disease, lupus erythematosus, microscopic colitis, microscopic polyarteritis, mixed connective tissue disease, Muckle-Wells syndrome, multiple sclerosis, myasthenia gravis, opsoclonus myoclonus syndrome, optic neuritis, ord's

thyroiditis, pemphigus, polyarteritis nodosa, polymyalgia, rheumatoid arthritis, Reiter's syndrome, Sjogren's syndrome, temporal arteritis, Wegener's granulomatosis, warm autoimmune haemolytic anemia, interstitial cystitis, Lyme disease, morphea, psoriasis, sarcoidosis, scleroderma, ulcerative colitis, and vitiligo.

[1764] The methods and solid dosage forms described herein may be used to treat T-cell mediated hypersensitivity diseases having an inflammatory component. Such conditions include, but are not limited to, contact hypersensitivity, contact dermatitis (including that due to poison ivy), urticaria, skin allergies, respiratory allergies (hay fever, allergic rhinitis, house dustmite allergy) and gluten-sensitive enteropathy (Celiac disease).

[1765] Other immune disorders which may be treated with the methods and solid dosage forms include, for example, appendicitis, dermatitis, dermatomyositis, endocarditis, fibrositis, gingivitis, glossitis, hepatitis, hidradenitis suppurativa, iritis, laryngitis, mastitis, myocarditis, nephritis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, pneumonitis, prostatitis, pyelonephritis, and stomatitis, transplant rejection (involving organs such as kidney, liver, heart, lung, pancreas (e.g., islet cells), bone marrow, cornea, small bowel, skin allografts, skin homografts, and heart valve xenografts, sepsis, and graft vs host disease), acute pancreatitis, chronic pancreatitis, acute respiratory distress syndrome, Sexary's syndrome, congenital adrenal hyperplasia, nonsuppurative thyroiditis, hypercalcemia associated with cancer, pemphigus, bullous dermatitis herpetiformis, severe erythema multiforme, exfoliative dermatitis, seborrheic dermatitis, seasonal or perennial allergic rhinitis, bronchial asthma, contact dermatitis, atopic dermatitis, drug hypersensitivity reactions, allergic conjunctivitis, keratitis, herpes zoster ophthalmicus, iritis and iridocyclitis, chorioretinitis, optic neuritis, symptomatic sarcoidosis, fulminating or disseminated pulmonary tuberculosis chemotherapy, idiopathic thrombocytopenic purpura in adults, secondary thrombocytopenia in adults, acquired (autoimmune) haemolytic anemia, leukaemia and lymphomas in adults, acute leukaemia of childhood, regional enteritis, autoimmune vasculitis, multiple sclerosis, chronic obstructive pulmonary disease, solid organ transplant rejection, sepsis. Preferred treatments include treatment of transplant rejection, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, Type 1 diabetes, asthma, inflammatory bowel disease, systemic lupus erythematosus, psoriasis, chronic obstructive pulmonary disease, and inflammation accompanying infectious conditions (e.g., sepsis).

Metabolic Disorders

[1766] In some embodiments, the methods and solid dosage forms described herein relate to the treatment or prevention of a metabolic disease or disorder a, such as type II diabetes, impaired glucose tolerance, insulin resistance, obesity, hyperglycemia, hyperinsulinemia, fatty liver, non-alcoholic steatohepatitis, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, ketoacidosis, hypoglycemia, thrombotic disorders, dyslipidemia, non-alcoholic fatty liver disease (NAFLD), Nonalcoholic Steatohepatitis (NASH) or a related disease. In some embodiments, the related disease is cardiovascular disease, atherosclerosis, kidney disease, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, or edema. In some embodiments, the methods and pharmaceutical compositions described herein relate to the treatment of Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH).

[1767] The methods and solid dosage forms 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 metabolic disease or disorder, as well as any subject with an increased likelihood of acquiring a such a disease or disorder.

[1768] The solid dosage forms described herein can be used, for example, for preventing or treating (reducing, partially or completely, the adverse effects of) a metabolic disease, such as type II diabetes, impaired glucose tolerance, insulin resistance, obesity, hyperglycemia, hyperinsulinemia, fatty liver, non-alcoholic steatohepatitis, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, ketoacidosis, hypoglycemia, thrombotic disorders, dyslipidemia, non-alcoholic fatty liver disease (NAFLD), Nonalcoholic Steatohepatitis (NASH), or a related disease. In some embodiments, the related disease is cardiovascular disease, atherosclerosis, kidney disease, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, or edema.

[1769]

[1770] Cancer

[1771] In some embodiments, the methods and solid dosage forms described herein relate to the treatment of cancer. In some embodiments, any cancer can be treated using the methods described herein. Examples of cancers that may treated by methods and solid dosage forms described herein include, but are not limited to, cancer cells from the bladder,

blood, bone, bone marrow, brain, breast, colon, esophagus, gastrointestinal, gum, head, kidney, liver, lung, nasopharynx, neck, ovary, prostate, skin, stomach, testis, tongue, or uterus. In addition, the cancer may specifically be of the following histological type, though it is not limited to these: neoplasm, malignant; carcinoma; carcinoma, undifferentiated; giant and spindle cell carcinoma; small cell carcinoma; papillary carcinoma; squamous cell carcinoma; lymphoepithelial carcinoma; basal cell carcinoma; pilomatrix carcinoma; transitional cell carcinoma; papillary transitional cell carcinoma; adenocarcinoma; gastrinoma, malignant; cholangiocarcinoma; hepatocellular carcinoma; combined hepatocellular carcinoma and cholangiocarcinoma; trabecular adenocarcinoma; adenoid cystic carcinoma; adenocarcinoma in adenomatous polyp; adenocarcinoma, familial polyposis coli; solid carcinoma; carcinoid tumor, malignant; bronchiole-alveolar adenocarcinoma; papillary adenocarcinoma; chromophobe carcinoma; acidophil carcinoma; oxyphilic adenocarcinoma; basophil carcinoma; clear cell adenocarcinoma; granular cell carcinoma; follicular adenocarcinoma; papillary and follicular adenocarcinoma; nonencapsulating sclerosing carcinoma; adrenal cortical carcinoma; endometrioid carcinoma; skin appendage carcinoma; apocrine adenocarcinoma; sebaceous adenocarcinoma; ceruminous adenocarcinoma; mucoepidermoid carcinoma; cystadenocarcinoma; papillary cystadenocarcinoma; papillary serous cystadenocarcinoma; mucinous cystadenocarcinoma; mucinous adenocarcinoma; signet ring cell carcinoma; infiltrating duct carcinoma; medullary carcinoma; lobular carcinoma; inflammatory carcinoma; paget's disease, mammary; acinar cell carcinoma; adenosquamous carcinoma; adenocarcinoma w/squamous metaplasia; thymoma, malignant; ovarian stromal tumor, malignant; thecoma, malignant; granulosa cell tumor, malignant; and rhabdomyosarcoma, malignant; sertoli cell carcinoma; leydig cell tumor, malignant; lipid cell tumor, malignant; paraganglioma, malignant; extra-mammary paraganglioma, malignant; pheochromocytoma; glomangiosarcoma; malignant melanoma; amelanotic melanoma; superficial spreading melanoma; malignant melanoma in giant pigmented nevus; epithelioid cell melanoma; blue nevus, malignant; sarcoma; fibrosarcoma; fibrous histiocytoma, malignant; myxosarcoma; liposarcoma; leiomyosarcoma; rhabdomyosarcoma; embryonal rhabdomyosarcoma; alveolar rhabdomyosarcoma; stromal sarcoma; mixed tumor, malignant; mullerian mixed tumor; nephroblastoma; hepatoblastoma; carcinosarcoma; mesenchymoma, malignant; brenner tumor, malignant; phyllodes tumor, malignant; synovial sarcoma; mesothelioma, malignant; dysgerminoma; embryonal carcinoma; teratoma, malignant; struma ovarii,

malignant; choriocarcinoma; mesonephroma, malignant; hemangiosarcoma; hemangioendothelioma, malignant; kaposi's sarcoma; hemangiopericytoma, malignant; lymphangiosarcoma; osteosarcoma; juxtacortical osteosarcoma; chondrosarcoma; chondroblastoma, malignant; mesenchymal chondrosarcoma; giant cell tumor of bone; ewing's sarcoma; odontogenic tumor, malignant; ameloblastic odontosarcoma; ameloblastoma, malignant; ameloblastic fibrosarcoma; pinealoma, malignant; chordoma; glioma, malignant; ependymoma; astrocytoma; protoplasmic astrocytoma; fibrillary astrocytoma; astroblastoma; glioblastoma; oligodendroglioma; oligodendroblastoma; primitive neuroectodermal; cerebellar sarcoma; ganglioneuroblastoma; neuroblastoma; retinoblastoma; olfactory neurogenic tumor; meningioma, malignant; neurofibrosarcoma; neurilemmoma, malignant; granular cell tumor, malignant; malignant lymphoma; Hodgkin's disease; Hodgkin's lymphoma; paragranuloma; malignant lymphoma, small lymphocytic; malignant lymphoma, large cell, diffuse; malignant lymphoma, follicular; mycosis fungoides; other specified non-Hodgkin's lymphomas; malignant histiocytosis; multiple myeloma; mast cell sarcoma; immunoproliferative small intestinal disease; leukemia; lymphoid leukemia; plasma cell leukemia; erythroleukemia; lymphosarcoma cell leukemia; myeloid leukemia; basophilic leukemia; eosinophilic leukemia; monocytic leukemia; mast cell leukemia; megakaryoblastic leukemia; myeloid sarcoma; and hairy cell leukemia.

[1772] In some embodiments, the cancer comprises breast cancer (e.g., triple negative breast cancer).

[1773] In some embodiments, the cancer comprises colorectal cancer (e.g., microsatellite stable (MSS) colorectal cancer).

[1774] In some embodiments, the cancer comprises renal cell carcinoma.

[1775] In some embodiments, the cancer comprises lung cancer (e.g., non small cell lung cancer).

[1776] In some embodiments, the cancer comprises bladder cancer.

[1777] In some embodiments, the cancer comprises gastroesophageal cancer.

[1778] In some embodiments, the methods and solid dosage forms provided herein relate to the treatment of a leukemia. The term "leukemia" includes broadly progressive, malignant diseases of the hematopoietic organs/systems and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Non-limiting examples of leukemia diseases include, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic

leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemic leukemia, basophilic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, undifferentiated cell leukemia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblastic leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, plasmacytic leukemia, and promyelocytic leukemia.

[1779] In some embodiments, the methods and solid dosage forms provided herein relate to the treatment of a carcinoma. The term "carcinoma" refers to a malignant growth made up of epithelial cells tending to infiltrate the surrounding tissues, and/or resist physiological and non-physiological cell death signals and gives rise to metastases. Non-limiting exemplary types of carcinomas include, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiennoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniform carcinoma, gelatinous carcinoma, giant cell carcinoma, signet-ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tuberous carcinoma, verrucous carcinoma, carcinoma villosum, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular

carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypernephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhus carcinoma, and carcinoma scroti.

[1780] In some embodiments, the methods and solid dosage forms provided herein relate to the treatment of a sarcoma. The term "sarcoma" generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar, heterogeneous, or homogeneous substance. Sarcomas include, but are not limited to, chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, and telangiectatic sarcoma.

[1781] Additional exemplary neoplasias that can be treated using the methods and solid dosage forms described herein include Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, breast cancer, ovarian cancer, lung cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, small-cell lung tumors, primary brain tumors, stomach cancer, colon cancer, malignant pancreatic insulanoma, malignant carcinoid, premalignant skin lesions, testicular cancer, lymphomas,

thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, cervical cancer, endometrial cancer, plasmacytoma, colorectal cancer, rectal cancer, and adrenal cortical cancer.

[1782] In some embodiments, the cancer treated is a melanoma. The term "melanoma" is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Non-limiting examples of melanomas are Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, nodular melanoma subungual melanoma, and superficial spreading melanoma.

[1783] Particular categories of tumors that can be treated using methods and solid dosage forms described herein include lymphoproliferative disorders, breast cancer, ovarian cancer, prostate cancer, cervical cancer, endometrial cancer, bone cancer, liver cancer, stomach cancer, colon cancer, pancreatic cancer, cancer of the thyroid, head and neck cancer, cancer of the central nervous system, cancer of the peripheral nervous system, skin cancer, kidney cancer, as well as metastases of all the above. Particular types of tumors include hepatocellular carcinoma, hepatoma, hepatoblastoma, rhabdomyosarcoma, esophageal carcinoma, thyroid carcinoma, ganglioblastoma, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, Ewing's tumor, leiomyosarcoma, rhabdotheliosarcoma, invasive ductal carcinoma, papillary adenocarcinoma, melanoma, pulmonary squamous cell carcinoma, basal cell carcinoma, adenocarcinoma (well differentiated, moderately differentiated, poorly differentiated or undifferentiated), bronchioloalveolar carcinoma, renal cell carcinoma, hypernephroma, hypernephroid adenocarcinoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, testicular tumor, lung carcinoma including small cell, non-small and large cell lung carcinoma, bladder carcinoma, glioma, astrocyoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, retinoblastoma, neuroblastoma, colon carcinoma, rectal carcinoma, hematopoietic malignancies including all types of leukemia and lymphoma including: acute myelogenous leukemia, acute myelocytic leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, mast cell leukemia, multiple myeloma, myeloid lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, plasmacytoma, colorectal cancer, and rectal cancer.

[1784] Cancers treated in certain embodiments also include precancerous lesions, e.g., actinic keratosis (solar keratosis), moles (dysplastic nevi), actinic cheilitis (farmer's lip), cutaneous horns, Barrett's esophagus, atrophic gastritis, dyskeratosis congenita, sideropenic dysphagia, lichen planus, oral submucous fibrosis, actinic (solar) elastosis and cervical dysplasia.

[1785] Cancers treated in some embodiments include non-cancerous or benign tumors, e.g., of endodermal, ectodermal or mesenchymal origin, including, but not limited to, cholangioma, colonic polyp, adenoma, papilloma, cystadenoma, liver cell adenoma, hydatidiform mole, renal tubular adenoma, squamous cell papilloma, gastric polyp, hemangioma, osteoma, chondroma, lipoma, fibroma, lymphangioma, leiomyoma, rhabdomyoma, astrocytoma, nevus, meningioma, and ganglioneuroma.

Other Diseases and Disorders

[1786] In some embodiments, the methods and solid dosage forms described herein relate to the treatment of liver diseases. Such diseases include, but are not limited to, Alagille Syndrome, Alcohol-Related Liver Disease, Alpha-1 Antitrypsin Deficiency, Autoimmune Hepatitis, Benign Liver Tumors, Biliary Atresia, Cirrhosis, Galactosemia, Gilbert Syndrome, Hemochromatosis, Hepatitis A, Hepatitis B, Hepatitis C, Hepatic Encephalopathy, Intrahepatic Cholestasis of Pregnancy (ICP), Lysosomal Acid Lipase Deficiency (LAL-D), Liver Cysts, Liver Cancer, Newborn Jaundice, Primary Biliary Cholangitis (PBC), Primary Sclerosing Cholangitis (PSC), Reye Syndrome, Type I Glycogen Storage Disease, and Wilson Disease.

[1787] The methods and solid dosage forms described herein may be used to treat neurodegenerative and neurological diseases. In certain embodiments, the neurodegenerative and/or neurological disease is Parkinson's disease, Alzheimer's disease, prion disease, Huntington's disease, motor neuron diseases (MND), spinocerebellar ataxia, spinal muscular atrophy, dystonia, idiopathic intracranial hypertension, epilepsy, nervous system disease, central nervous system disease, movement disorders, multiple sclerosis, encephalopathy, peripheral neuropathy or post-operative cognitive dysfunction.

Dysbiosis

[1788] In recent years, it has become increasingly clear that the gut microbiome (also called the "gut microbiota") can have a significant impact on an individual's health

through microbial activity and influence (local and/or distal) on immune and other cells of the host (Walker, W.A., Dysbiosis. The Microbiota in Gastrointestinal Pathophysiology. Chapter 25. 2017; Weiss and Thierry, Mechanisms and consequences of intestinal dysbiosis. *Cellular and Molecular Life Sciences*. (2017) 74(16):2959-2977. Zurich Open Repository and Archive, doi: <https://doi.org/10.1007/s00018-017-2509-x>)).

[1789] A healthy host-gut microbiome homeostasis is sometimes referred to as a “eubiosis” or “normobiosis,” whereas a detrimental change in the host microbiome composition and/or its diversity can lead to an unhealthy imbalance in the microbiome, or a “dysbiosis” (Hooks and O’Malley. *Dysbiosis and its discontents*. American Society for Microbiology. Oct 2017. Vol. 8. Issue 5. mBio 8:e01492-17. <https://doi.org/10.1128/mBio.01492-17>). Dysbiosis, and associated local or distal host inflammatory or immune effects, may occur where microbiome homeostasis is lost or diminished, resulting in: increased susceptibility to pathogens; altered host bacterial metabolic activity; induction of host proinflammatory activity and/or reduction of host anti-inflammatory activity. Such effects are mediated in part by interactions between host immune cells (e.g., T cells, dendritic cells, mast cells, NK cells, intestinal epithelial lymphocytes (IEC), macrophages and phagocytes) and cytokines, and other substances released by such cells and other host cells.

[1790] A dysbiosis may occur within the gastrointestinal tract (a “gastrointestinal dysbiosis” or “gut dysbiosis”) or may occur outside the lumen of the gastrointestinal tract (a “distal dysbiosis”). Gastrointestinal dysbiosis is often associated with a reduction in integrity of the intestinal epithelial barrier, reduced tight junction integrity and increased intestinal permeability. Citi, S. Intestinal Barriers protect against disease, *Science* 359:1098-99 (2018); Srinivasan et al., TEER measurement techniques for in vitro barrier model systems. *J. Lab. Autom.* 20:107-126 (2015). A gastrointestinal dysbiosis can have physiological and immune effects within and outside the gastrointestinal tract.

[1791] The presence of a dysbiosis has been associated with a wide variety of diseases and conditions including: infection, cancer, autoimmune disorders (e.g., systemic lupus erythematosus (SLE)) or inflammatory disorders (e.g., functional gastrointestinal disorders such as inflammatory bowel disease (IBD), ulcerative colitis, and Crohn’s disease), neuroinflammatory diseases (e.g., multiple sclerosis), transplant disorders (e.g., graft-versus-host disease), fatty liver disease, type I diabetes, rheumatoid arthritis, Sjögren’s syndrome, celiac disease, cystic fibrosis, chronic obstructive pulmonary disorder (COPD),

and other diseases and conditions associated with immune dysfunction. Lynch et al., The Human Microbiome in Health and Disease, *N. Engl. J. Med.* 375:2369-79 (2016), Carding et al., Dysbiosis of the gut microbiota in disease. *Microb. Ecol. Health Dis.* (2015); 26: 10: 3402/mehd.v26.2619; Levy et al, Dysbiosis and the Immune System, *Nature Reviews Immunology* 17:219 (April 2017)

[1792] Exemplary solid dosage forms disclosed herein can treat a dysbiosis and its effects by modifying the immune activity present at the site of dysbiosis. As described herein, such compositions can modify a dysbiosis via effects on host immune cells, resulting in, e.g., an increase in secretion of anti-inflammatory cytokines and/or a decrease in secretion of pro-inflammatory cytokines, reducing inflammation in the subject recipient or via changes in metabolite production.

[1793] Exemplary solid dosage forms disclosed herein that are useful for treatment of disorders associated with a dysbiosis contain one or more types of immunomodulatory bacteria (e.g., anti-inflammatory bacteria) and/or mEVs (microbial extracellular vesicles) derived from such bacteria. Such compositions are capable of affecting the recipient host's immune function, in the gastrointestinal tract, and/or a systemic effect at distal sites outside the subject's gastrointestinal tract.

[1794] Exemplary solid dosage forms disclosed herein that are useful for treatment of disorders associated with a dysbiosis contain a population of immunomodulatory bacteria of a single bacterial species (e.g., a single strain) (e.g., anti-inflammatory bacteria) and/or mEVs derived from such bacteria. Such compositions are capable of affecting the recipient host's immune function, in the gastrointestinal tract, and /or a systemic effect at distal sites outside the subject's gastrointestinal tract.

[1795] In one embodiment, solid dosage forms containing an isolated population of immunomodulatory bacteria (e.g., anti-inflammatory bacterial cells) and/or mEVs derived from such bacteria are administered (e.g., orally) to a mammalian recipient in an amount effective to treat a dysbiosis and one or more of its effects in the recipient. The dysbiosis may be a gastrointestinal tract dysbiosis or a distal dysbiosis.

[1796] In another embodiment, solid dosage forms of the instant invention can treat a gastrointestinal dysbiosis and one or more of its effects on host immune cells, resulting in an increase in secretion of anti-inflammatory cytokines and/or a decrease in secretion of pro-inflammatory cytokines, reducing inflammation in the subject recipient.

[1797] In another embodiment, the solid dosage forms can treat a gastrointestinal dysbiosis and one or more of its effects by modulating the recipient immune response via cellular and cytokine modulation to reduce gut permeability by increasing the integrity of the intestinal epithelial barrier.

[1798] In another embodiment, the solid dosage forms can treat a distal dysbiosis and one or more of its effects by modulating the recipient immune response at the site of dysbiosis via modulation of host immune cells.

[1799] Other exemplary solid dosage forms are useful for treatment of disorders associated with a dysbiosis, which compositions contain one or more types of bacteria and/or mEVs capable of altering the relative proportions of host immune cell subpopulations, *e.g.*, subpopulations of T cells, immune lymphoid cells, dendritic cells, NK cells and other immune cells, or the function thereof, in the recipient.

[1800] Other exemplary solid dosage forms are useful for treatment of disorders associated with a dysbiosis, which compositions contain a population of immunomodulatory bacteria and/or mEVs of a single bacterial species, *e.g.*, a single strain) capable of altering the relative proportions of immune cell subpopulations, *e.g.*, T cell subpopulations, immune lymphoid cells, NK cells and other immune cells, or the function thereof, in the recipient subject.

[1801] In one embodiment, the invention provides methods of treating a gastrointestinal dysbiosis and one or more of its effects by orally administering to a subject in need thereof a solid dosage form which alters the microbiome population existing at the site of the dysbiosis. The solid dosage forms can contain one or more types of immunomodulatory bacteria and/or mEVs or a population of immunomodulatory bacteria and/or mEVs of a single bacterial species (*e.g.*, a single strain).

[1802] In one embodiment, the invention provides methods of treating a distal dysbiosis and one or more of its effects by orally administering to a subject in need thereof a solid dosage form which alters the subject's immune response outside the gastrointestinal tract. The solid dosage forms can contain one or more types of immunomodulatory bacteria and/or mEVs or a population of immunomodulatory bacteria and/or mEVs of a single bacterial species (*e.g.*, a single strain).

[1803] In exemplary embodiments, solid dosage forms useful for treatment of disorders associated with a dysbiosis stimulate secretion of one or more anti-inflammatory cytokines by host immune cells. Anti-inflammatory cytokines include, but are not limited

to, IL-10, IL-13, IL-9, IL-4, IL-5, TGF β , and combinations thereof. In other exemplary embodiments, solid dosage forms useful for treatment of disorders associated with a dysbiosis that decrease (e.g., inhibit) secretion of one or more pro-inflammatory cytokines by host immune cells. Pro-inflammatory cytokines include, but are not limited to, IFN γ , IL-12p70, IL-1 α , IL-6, IL-8, MCP1, MIP1 α , MIP1 β , TNF α , and combinations thereof. Other exemplary cytokines are known in the art and are described herein.

[1804] In another aspect, the invention provides a method of treating or preventing a disorder associated with a dysbiosis in a subject in need thereof, comprising administering (e.g., orally administering) to the subject a solid dosage form in the form of a probiotic or medical food comprising bacteria and/or mEVs in an amount sufficient to alter the microbiome at a site of the dysbiosis, such that the disorder associated with the dysbiosis is treated.

[1805] In another embodiment, a solid dosage form of the instant invention in the form of a probiotic or medical food may be used to prevent or delay the onset of a dysbiosis in a subject at risk for developing a dysbiosis.

Methods of Making Enhanced Bacteria

[1806] In certain aspects, provided herein are methods of making engineered bacteria for the production of the bacteria and/or mEVs (such as smEVs and/or pmEVs) described herein. In some embodiments, the engineered bacteria are modified to enhance certain desirable properties. For example, in some embodiments, the engineered bacteria are modified to enhance the immunomodulatory and/or therapeutic effect of the bacteria and/or mEVs (such as smEVs and/or pmEVs) (e.g., either alone or in combination with another pharmaceutical agent), to reduce toxicity and/or to improve bacterial and/or mEV (such as smEV and/or pmEV) manufacturing (e.g., higher oxygen tolerance, improved freeze-thaw tolerance, shorter generation times). The engineered bacteria may be produced using any technique known in the art, including but not limited to site-directed mutagenesis, transposon mutagenesis, knock-outs, knock-ins, polymerase chain reaction mutagenesis, chemical mutagenesis, ultraviolet light mutagenesis, transformation (chemically or by electroporation), phage transduction, directed evolution, CRISPR/Cas9, or any combination thereof.

[1807] In some embodiments of the methods provided herein, the bacterium is modified by directed evolution. In some embodiments, the directed evolution comprises

exposure of the bacterium to an environmental condition and selection of bacterium with improved survival and/or growth under the environmental condition. In some embodiments, the method comprises a screen of mutagenized bacteria using an assay that identifies enhanced bacterium. In some embodiments, the method further comprises mutagenizing the bacteria (e.g., by exposure to chemical mutagens and/or UV radiation) or exposing them to a pharmaceutical agent (e.g., antibiotic) followed by an assay to detect bacteria having the desired phenotype (e.g., an *in vivo* assay, an *ex vivo* assay, or an *in vitro* assay).

Gamma- Irradiation: Sample Protocol:

[1808] Powders are gamma-irradiated at 17.5 kGy radiation unit at ambient temperature. Frozen biomasses are gamma-irradiated at 25 kGy radiation unit in the presence of dry ice.

Frozen Biomass Preparation: Sample Protocol

[1809] After a desired level of bacterial culture growth is achieved, centrifuge cultures, discard the supernatant, leaving the pellet as dry as possible. Vortex the pellet to loosen the biomass. Resuspend pellet in desired cryoprotectant solution, transfer to cryogenic tube and snap freeze in liquid nitrogen. Store in -80 degree C freezer.

Powder Preparation: Sample Protocol

[1810] After desired level of bacterial culture growth is achieved, centrifuge cultures, discard the supernatant, leaving the pellet as dry as possible. Resuspend pellet in desired cryoprotectant solution to create a formulated cell paste. The cryoprotectant may contain, e.g., maltodextrin, sodium ascorbate, sodium glutamate, and/or calcium chloride. Load the formulated cell paste onto stainless steel trays and load into a freeze drier, e.g., operating in automated mode with defined cycle parameters. The freeze dried product is fed into a milling machine and the resulting powder is collected.

[1811] Powders are stored (e.g., in vacuum sealed bags) at 2-8 degrees C (e.g., at 4 degrees C), e.g., in a desiccator.

Examples

Example 1: Preparation of *Lactococcus lactis* spp. *Cremoris* powder

[1812] The fermentation broth was harvested by continuous centrifugation with a flow rate of 2500 L/h and expulsion time of 150 seconds. The concentrated cells were collected and the supernatant is discarded.

[1813] The cryoprotectant solution components were maltodextrin (16% w/w), sodium ascorbate (8% w/w), sodium glutamate (8% w/w), and calcium chloride (8% w/w). They were first dissolved in a mixing tank and pasteurized; the solution was cooled to 4-10 degrees C.

[1814] The cooled cryoprotectant solution was added to the concentrated cells at a ratio of 25% (w/w) and mixed to give a formulated cell paste.

[1815] The formulated cell paste was loaded onto multiple stainless-steel trays. The freeze-drier was operated in an automated mode with defined cycle parameters. At the end of cycle, the freeze-dried product was removed from the tray and stored in multiple polyethylene bags prior to milling.

[1816] The freeze-dried product was fed into a milling machine and collected into a double polyethylene bags. The bags were checked with a metal detector (given the milling machine is a metal blender) and then stored at 2-8m degrees C prior to final packaging.

[1817] Freeze-dried powder (1 kg aliquots) was placed into a polyethylene bag which was then packed into a PET-AL-PE foil pouch and heat sealed. Long term storage conditions for the finished pouches were 2-8 degrees C.

Example 2: Enteric coated minitabets significantly enhance *L. lactis* spp. *Cremoris* pharmacological activity at low doses

[1818] Method: Mice were immunized intra-dermally with a KLH-DTH emulsion on Day 0. Mice were dosed with either dexamethasone intraperitoneally (17ug per mouse in 100ul of PBS) as a positive control, or orally with sucrose vehicle alone as a negative control, or with *Lactococcus lactis* spp. *Cremoris* powder resuspended in a sucrose delivery buffer or with enteric coated 2mm minitabets containing different doses of *Lactococcus lactis* spp. *Cremoris* powder (0.1mg, 0.35 mg, 1 mg, or 3.5 mg) (see Figure 1) on days 1-8. The coating is provided in Table 5. On day 8, mice were challenged intra-dermally in the left ear with 10ug of KLH and 24 hours later the change in ear thickness from baseline was assessed.

[1819] Results: When delivered in enteric coated minitabets, 3.5mg and 1mg doses of *L. lactis spp. Cremoris* powder led to a significant reduction in ear swelling compared to vehicle control.

Table 5: Enteric coating (on dry basis) on *L. lactis spp. Cremoris* minitabets (2mm)

Component	Enteric coating (mg)	Enteric coating (mg/cm ² surface)
EUDRAGIT® L 30 D-55	0.97	6.6
Triethylcitrate	0.19	1.32
Talc	0.48	3.3

Example 3: Methacrylic acrylate copolymer coating

[1820] Table 6 presents a coating suspension including Kollicoat MAE 100P as the enteric polymer, plasticizers (1,2-propylene glycol, triethyl citrate or polyethylene glycols) ranges from 10-25% based on the polymer weight, and anti-tacking agent ranges from 15-25% based on the polymer weight.

Table 6: Kollicoat® Coating Suspension Composition

Excipient	Function	(% w/w)
Kollicoat® MAE 100P	Enteric Polymer	15.00
Triethyl Citrate (TEC)	Plasticizer	2.25
Talc	Anti-tacking agent/Pigment	3.00
Water		79.75
Total		100.00

Coating Suspension Preparation Procedure

- Divided the water into three portions
- Dissolved TEC into portion 1 water (solution 1)
- Re-dispersed polymer into portion 2 water slowly, stirred with a magnetic stirring bar for 2 hrs, ensured polymer was fully hydrated/ dispersed with no lumps (suspension 2)
- Dispensed talc into portion 3 water slowly to hydrate, homogenized the talc suspension with a Silverson high shear homogenizer for 3 minutes at 6000RPM to ensure no lump (suspension 3)
- Added solution 1 into suspension 2, followed by the addition of suspension 3

- f. Mixed for 15 minutes and pass the suspension through USP#60 mesh
- g. The final suspension was subject for coating

Coating Equipment and Processing Parameters

Table 7: Process 1 (Mini tablets)

Coating Equipment	VFC-Lab Micro Fluid Bed
Batch size	20 g
Nozzle diameter	0.8mm
Spray rate	0.5-0.8 g/min
Nozzle air	21-25 PSI
Inlet air Tm	50-55°C
Exhaust Tm	34-37°C
Pump rate	10-12 RPM

Table 8: Process 2 (Single Tablet)

Coating Equipment	O'hara LC M10 Pan Coater
Batch size	650 g
Nozzle diameter	0.8 mm
Spray rate	5 g/min
Atomization Air Pressure	25.4 PSI
Pattern Air Pressure	20.5 PSI
Supply Air Volume	90 cfm
Inlet air Tm	47-50°C
Exhaust Tm	35-38°C
Drum Size	12 in
Drum Speed	12 RPM

Example 4: Coating Tablets

[1821] Tablets of *Prevotella* Strain B 50329 (NRRL accession number B 50329) and tablets of *Veillonella* bacteria (deposited as ATCC designation number PTA-125691) were prepared. Placebo tablets were also coated.

[1822] The tablets of *Prevotella* Strain B 50329 were 650 mg. Placebo tablets were also prepared.

[1823] The tablets of the *Veillonella* strain were 400 mg. Tablets were prepared in two strengths (high and low doses). Placebo tablets were also prepared.

[1824] Table 9 provides the formulation compositions of the coating suspensions.

Table 9: Formulation compositions of coating suspensions

Material	Sub-coat	Top-coat (Enteric)
	Composition % (w/w)	Composition % (w/w)
Kollidon MAE 100P	-	15.00
TEC	-	2.25
Talc	-	3.00
Additional Water	-	79.75
Opadry II White Product code: 85F18422	15.0	-
WFI	85.0	-
Total	100.0	100.0

[1825] The tablets were coated as follows.

Coating Suspension Manufacturing Procedure:

1. Divided the water into two portions and dispensed part one of the water for injection into a tared stainless-steel vessel.
2. Weighed and dispensed the Triethyl Citrate into a suitable tared container.
3. Added the dispensed Triethyl Citrate to the water while mixing with the overhead stirrer.
4. Weighed and dispensed the Talc into a suitable tared container.
5. Added the dispensed Talc slowly to the water / Triethyl Citrate solution, while mixing with the overhead stirrer.
6. Once the Talc was fully hydrated, transferred the vessel to the Silverson. Homogenized for a minimum of 10 minutes, ensuring that all Talc had been fully dispersed / homogenized, without any lumps and with no material stuck to the mixer head.
7. Dispensed Part Two of the Water for injection into a tared stainless-steel vessel.
8. Weighed and dispensed the Kollicoat into a suitable tared container.
9. Added the dispensed Kollicoat slowly to the water from step 7 while mixing with the overhead stirrer.
10. Continued mixing until all the Kollicoat had been added and is fully hydrated and dispersed without any lumps and with no material stuck to the paddle.

11. Transferred the Water/Triethyl Citrate/Talc suspension to the overhead stirrer and started mixing.
12. Whilst continuing to mix, transferred the Kollicoat suspension into the vessel. Mixed for a minimum of 45 minutes at an appropriate speed to form a vortex without any aeration.
13. Passed the coating suspension through a 500µm sieve into a stainless-steel vessel. Ensured all solids passed through the mesh.

[1826] Table 10 provides the process parameters for enteric coating.

Table 10: Process Parameters of Enteric coating

	Active	Placebo
Bed Temperature (°C)	30 - 35	30 - 35
Drum Speed (rpm)	17	17
Inlet Airflow (m ³ /hr)	170	170 - 180
Cabinet Pressure (Pa)	- 60	- 60
Inlet Air Temperature (°C)	46 - 49	46 - 52
Atomising Air Pressure (bar)	1.6	1.6
Spray Rate	<i>6 g/min/kg - 5.9 g/min consistent – 1450 capsules</i>	<i>6 g/min/kg - 5.8 g/min consistent – 1456 tablets</i>
Distance to bed	<i>15 cm</i>	<i>15 cm</i>
Angle to capsule bed	<i>90 – 15° to the bed</i>	<i>90 – 15° to the bed</i>
Baffles	<i>No (batch too big)</i>	<i>No (batch too big)</i>
Nozzle size	<i>0.8 mm</i>	<i>0.8 mm</i>
Drum size	<i>15” drum</i>	<i>15” drum</i>
Coating efficiency overall	<i>93.5%</i>	<i>96.0%</i>

[1827] Table 11 provides the disintegration results for the Prevotella Strain B 50329 (active) and placebo tablets.

Table 11: *Prevotella* Strain B Disintegration Results

Batch Reference	Storage Condition	Time Point (Months)	Results (hh:mm:ss)	
			0.1 M HCl	6.8 pH Buffer
Active	2-8 °C	Initial	DND*	First: 00:12:56 Last: 00:14:36
Placebo			DND	First: 00:10:21 Last: 00:14:10
Active		T= 1 month	DND	First: 00:13:09 Last: 00:15:11
Placebo			DND	First: 00:06:21 Last: 00:07:41
Active	25 °C, 60% RH	T= 1 month	DND	First: 00:12:18 Last: 00:15:18
Placebo			DND	First: 00:06:26 Last: 00:08:23
Active	30 °C, 65% RH	T= 1 month	DND	First: 00:14:06 Last: 00:15:50
Placebo			DND	First: 00:07:05 Last: 00:09:04
Active	40 °C, 75% RH	T= 1 month	DND	First: 00:11:47 Last: 00:13:07
Placebo			DND	First: 00:08:05 Last: 00:09:16

DND*: Did not disintegrate; RH: relative humidity

[1828] Table 12 provides the disintegration results for the high and low dose tablets of the *Veillonella* strain.

Table 12: *Veillonella* Tablets Disintegration Results

Batch Reference	Storage Condition	Time Point (Months)	Results (hh: mm: ss)	
			0.1 M HCl	6.8 pH Buffer
High Dose	2-8 °C	Initial	DND*	00:19:08
Low Dose	2-8 °C	Initial	DND*	00:09:05

*DND – Did not disintegrate

Example 5: Coating Capsules

[1829] Capsules were prepared for:

- *Prevotella* Strain B 50329 (NRRL accession number B 50329)
- *Veillonella* bacteria (deposited as ATCC designation number PTA-125691)
- *Lactococcus lactis cremoris* Strain A (deposited as ATCC designation number PTA-125368)
- *Bifidobacterium* bacteria (deposited as ATCC designation number PTA-125097)

[1830] The capsules were all size 0.

[1831] Capsules of the *Veillonella* strain were prepared in two strengths (high and low doses).

[1832] Capsules were banded with an HPMC-based banding solution prior to enteric coating.

[1833] Table 13 provides the formulation compositions of the coating suspensions.

Table 13: Composition of Coating Solutions

Coating Suspension Ingredients			
Eudragit L30-D55	Enteric Coating Agent	39.72	USP / Ph. Eur.
Triethyl citrate	Plasticizer	2.31	USP / Ph. Eur.
Talc	Antiadhesive	5.78	USP / Ph. Eur.
Water for Injection ^a	Solvent	52.19	USP / Ph. Eur.

^a Removed during processing

[1834] The capsules were coated as follows:

Coating Suspension Preparation Procedure:

1. Weighed and dispensed the Water for injection into a tared stainless-steel vessel.
2. Weighed and dispensed the Triethyl Citrate into a suitable tared container.
3. Weighed and dispensed the Talc into a suitable tared container.
4. Added the Triethyl Citrate and Talc to the water and dispersed by stirring gently with a palette knife until there was no talc floating on the surface of the water. Ensured that the talc was fully wetted before commencing stirring.
5. Homogenized using the Silverson mixer for a minimum of 10 mins.
6. Weighed and dispensed the Eudragit L30-D55 into a suitable tared container.

7. Stirred the Eudragit L30-D55 into the Triethyl Citrate / Talc suspension using an overhead mixer. Recorded the mixing speed. Maintained sufficient mixing to prevent further air ingress.
8. Continued mixing for a minimum of 30 minutes.
9. Passed the coating suspension through a 500µm sieve into a second stainless steel vessel.

[1835] Table 14 provides the process parameters of enteric coating.

Table 14: Process Parameters of Enteric Coating

Parameter	Settings
Bed Temperature (°C)	26-30
Inlet Airflow (m ³ /hr)	150-180
Drum Speed (RPM)	18
Cabinet Pressure (Pa)	– 60
Inlet Air Temperature (°C)	45
Atomising Air Pressure (bar)	1.4
Spray Rate	12 g/min/kg
Distance to bed	15 cm
Angle to capsule bed	90 – 15° to the bed
Nozzle size	0.8 mm
Drum size	15" drum

[1836] Table 15 provides the disintegration results for *Prevotella* Strain B capsules.

Table 15: Disintegration results (*Prevotella* Strain B)

Batch Reference	Storage Condition	Time Point (Months)	Results (hh: mm: ss)	
			0.1 M HCl	6.8 pH Buffer
Prevotella active	2-8 °C	Initial	DND*	00:10:10

DND*: Did not disintegrate

[1837] Table 16 provides the disintegration results for the *Veillonella* strain capsules.

Table 16: Disintegration Results (*Veillonella*)

Batch Reference	Storage Condition	Time Point (Months)	Results (hh:mm:ss)	
			0.1 M HCl	6.8 pH Buffer
Low dose	2-8 °C	Initial	DND*	First: 00:05:42 Last: 00:07:05
High dose		Initial	DND	First: 00:06:04 Last: 00:13:28

*DND – Did not disintegrate

Example 6: Representative Strains As Sources for EVs

[1838] Secreted microbial extracellular vesicles (smEVs) were isolated from the strains listed in Table J. Information on the Gram staining, cell wall structure, and taxonomic classification for each strain is also provided in Table J.

[1839] Bacteria of the taxonomic groups listed in Table J (e.g., class, order, family, genus, species or strain) can be used in the solid dosage forms described herein.

[1840] mEVs of bacteria of the taxonomic groups listed in Table J (e.g., class, order, family, genus, species or strain) can be used in the solid dosage forms described herein.

Table J: Strains from which extracellular vesicles (EVs) were isolated

Strain	Gram-stain	Cell envelope structure	Phylum	Class	Order	Family
<i>Parabacteroides distasonis</i> DRLU022118 A ILEUM-6	Gram-stain-negative	diderm	Bacteroidota	Bacteroidia	Bacteroidales	<i>Porphyromonadaceae</i>
<i>Parabacteroides goldsteinii</i> S4	Gram-stain-negative	diderm	Bacteroidota	Bacteroidia	Bacteroidales	<i>Porphyromonadaceae</i>
<i>Prevotella histicola</i>	Gram-stain-negative	diderm	Bacteroidota	Bacteroidia	Bacteroidales	<i>Prevotellaceae</i>
<i>Prevotella histicola</i>	Gram-stain-negative	diderm	Bacteroidota	Bacteroidia	Bacteroidales	<i>Prevotellaceae</i>
<i>Fournierella massiliensis</i> S10 GIMucosa-297	Gram-stain-negative	monoderm	Firmicutes	Clostridia	Eubacteriales	<i>Oscillospiraceae</i> (formerly <i>Ruminococcaceae</i>)
<i>Harryflintia acetispora</i> S4-M5	Gram-stain-negative	monoderm	Firmicutes	Clostridia	Eubacteriales	<i>Oscillospiraceae</i>
<i>Blautia massiliensis</i> S1046-4A5	Gram-stain-negative	monoderm	Firmicutes	Clostridia	Eubacteriales	<i>Lachnospiraceae</i>
<i>Mediterraneibacter</i> /[<i>Ruminococcus</i>] <i>gnavus</i> S10 GIMucosa-412	Gram-stain-negative	monoderm	Firmicutes	Clostridia	Eubacteriales	<i>Lachnospiraceae</i>
<i>Clostridioides difficile</i> S10 GImucosa-525	Gram-stain-positive	monoderm	Firmicutes	Clostridia	Eubacteriales	<i>Peptostreptococcaceae</i>
<i>Aminipila</i> sp. S16-M4	Gram-stain-positive	monoderm	Firmicutes	Clostridia	Eubacteriales	Clostridiales Family XIII/Incertae sedis 41/[Eubacteriales, no family]
<i>Megasphaera</i> sp. S29-N3	Gram-stain-negative	diderm	Firmicutes	Negativicutes	Veillonellales	<i>Veillonellaceae</i>
<i>Megasphaera</i> sp. S1007	Gram-stain-negative	diderm	Firmicutes	Negativicutes	Veillonellales	<i>Veillonellaceae</i>
<i>Selenomonas felix</i> S34N-300R	Gram-stain-negative	diderm	Firmicutes	Negativicutes	Selenomonadales	<i>Selenomonadaceae</i>
<i>Veillonella parvula</i> S14Ileum-201	Gram-stain-negative	diderm	Firmicutes	Negativicutes	Veillonellales	<i>Veillonellaceae</i>
<i>Propionispora</i> sp. DSM100705-1A	Gram-stain-negative	diderm	Firmicutes	Negativicutes	Selenomonadales	<i>Sporomusaceae</i>
<i>Rarimicrobium hominis</i> S24RS2-T2-5	Gram-stain-negative	diderm	Synergistota	Synergistia	Synergistales	<i>Synergistaceae</i>

<i>Cloacibacillus evryensis</i> S29-M8	Gram-stain-negative	<i>diderm</i>	Synergistota	Synergistia	Synergistales	<i>Synergistaceae</i>
<i>Veillonella parvula</i> S14-205	Gram-stain-negative	<i>diderm</i>	Firmicutes	Negativicutes	Veillonellales	<i>Veillonellaceae</i>
<i>Veillonella</i> sp/dispar ECD01-DP-201	Gram-stain-negative	<i>diderm</i>	Firmicutes	Negativicutes	Veillonellales	<i>Veillonellaceae</i>
<i>Veillonella parvula</i> /dispar ECD01-DP-223	Gram-stain-negative	<i>diderm</i>	Firmicutes	Negativicutes	Veillonellales	<i>Veillonellaceae</i>
<i>Veillonella parvula</i> S16 GIMucosa-95	Gram-stain-negative	<i>diderm</i>	Firmicutes	Negativicutes	Veillonellales	<i>Veillonellaceae</i>

Example 7: Delayed-type hypersensitivity (DTH) is an animal model

[1841] Delayed-type hypersensitivity (DTH) is an animal model of atopic dermatitis (or allergic contact dermatitis), as reviewed by Petersen et al. (In vivo pharmacological disease models for psoriasis and atopic dermatitis in drug discovery. *Basic & Clinical Pharm & Toxicology*. 2006. 99(2): 104-115; see also Irving C. Allen (ed.) *Mouse Models of Innate Immunity: Methods and Protocols*, *Methods in Molecular Biology*, 2013. vol. 1031, DOI 10.1007/978-1-62703-481-4_13). Several variations of the DTH model have been used and are well known in the art (Irving C. Allen (ed.). *Mouse Models of Innate Immunity: Methods and Protocols*, *Methods in Molecular Biology*. Vol. 1031, DOI 10.1007/978-1-62703-481-4_13, Springer Science + Business Media, LLC 2013).

[1842] DTH can be induced in a variety of mouse and rat strains using various haptens or antigens, for example an antigen emulsified with an adjuvant. DTH is characterized by sensitization as well as an antigen-specific T cell-mediated reaction that results in erythema, edema, and cellular infiltration – especially infiltration of antigen presenting cells (APCs), eosinophils, activated CD4⁺ T cells, and cytokine-expressing Th2 cells.

[1843] Generally, mice are primed with an antigen administered in the context of an adjuvant (e.g., Complete Freund's Adjuvant) in order to induce a secondary (or memory) immune response measured by swelling and antigen-specific antibody titer.

[1844] Dexamethasone, a corticosteroid, is a known anti-inflammatory that ameliorates DTH reactions in mice and serves as a positive control for suppressing inflammation in this model (Taube and Carlsten, Action of dexamethasone in the suppression of delayed-type hypersensitivity in reconstituted SCID mice. *Inflamm Res*. 2000. 49(10): 548-52). For the positive control group, a stock solution of 17 mg/mL of Dexamethasone is prepared on Day 0 by diluting 6.8 mg Dexamethasone in 400 μ L 96% ethanol. For each day of dosing, a working solution is prepared by diluting the stock solution 100x in sterile PBS to obtain a final concentration of 0.17 mg/mL in a septum vial for intraperitoneal dosing. Dexamethasone-treated mice receive 100 μ L Dexamethasone i.p. (5 mL/kg of a 0.17 mg/mL solution). Frozen sucrose serves as the negative control (vehicle).

[1845] Solid dosage forms are tested for their efficacy in the mouse model of DTH, either alone or in combination, with or without the addition of other anti-inflammatory

treatments. For example, 6-8 week old C57Bl/6 mice are obtained from Taconic (Germantown, NY), or other vendor. Groups of mice are administered four subcutaneous (s.c.) injections at four sites on the back (upper and lower) of antigen (e.g., Ovalbumin (OVA) or Keyhole Limpet Hemocyanin (KLH)) in an effective dose (e.g., 50ul total volume per site). For a DTH response, animals are injected intradermally (i.d.) in the ears under ketamine/xylazine anesthesia (approximately 50mg/kg and 5 mg/kg, respectively). Some mice serve as control animals. Some groups of mice are challenged with 10ul per ear (vehicle control (0.01% DMSO in saline) in the left ear and antigen (21.2 ug (12nmol) in the right ear) on day 8. To measure ear inflammation, the ear thickness of manually restrained animals is measured using a Mitutoyo micrometer. The ear thickness is measured before intradermal challenge as the baseline level for each individual animal. Subsequently, the ear thickness is measured two times after intradermal challenge, at approximately 24 hours and 48 hours (i.e., days 9 and 10).

[1846] Treatment with a solid dosage form is initiated at some point, either around the time of priming or around the time of DTH challenge. For example, a solid dosage form may be administered at the same time as the subcutaneous injections (day 0), or it may be administered prior to, or upon, intradermal injection. A solid dosage form is administered (e.g., orally) at varied doses and at defined intervals. Examples are provided in the above examples. Some mice may receive a solid dosage form every day (e.g., starting on day 0), while others may receive a solid dosage form at alternative intervals (e.g., every other day, or once every three days).

[1847] As an example, an emulsion of Keyhole Limpet Hemocyanin (KLH) and Complete Freund's Adjuvant (CFA) can be prepared freshly on the day of immunization (day 0). To this end, 8 mg of KLH powder is weighed and is thoroughly re-suspended in 16 mL saline. An emulsion is prepared by mixing the KLH/saline with an equal volume of CFA solution (e.g., 10 mL KLH/saline + 10 mL CFA solution) using syringes and a luer lock connector. KLH and CFA are mixed vigorously for several minutes to form a white-colored emulsion to obtain maximum stability. A drop test is performed to check if a homogenous emulsion is obtained.

[1848] On day 0, C57Bl/6J female mice, approximately 7 weeks old, are primed with KLH antigen in CFA by subcutaneous immunization (4 sites, 50 µL per site). A solid dosage form is administered as described herein.

[1849] On day 8, mice are challenged intradermally (i.d.) with 10 µg KLH in saline (in a volume of 10 µL) in the left ear. Ear pinna thickness is measured at 24 hours following antigen challenge. The effectiveness of a solid dosage form at suppressing inflammation is determined by ear thickness.

[1850] For future inflammation studies, some groups of mice may be treated with anti-inflammatory agent(s) (e.g., anti-CD154, blockade of members of the TNF family, or other treatment), and/or an appropriate control (e.g., vehicle or control antibody) at various timepoints and at effective doses.

[1851] At various timepoints, serum samples may be taken. Other groups of mice may be sacrificed and lymph nodes, spleen, mesenteric lymph nodes (MLN), the small intestine, colon, and other tissues may be removed for histology studies, ex vivo histological, cytokine and/or flow cytometric analysis using methods known in the art. Some mice are exsanguinated from the orbital plexus under O₂/CO₂ anesthesia and ELISA assays performed.

[1852] Tissues may be dissociated using dissociation enzymes according to the manufacturer's instructions. Cells are stained for analysis by flow cytometry using techniques known in the art. Staining antibodies can include anti-CD11c (dendritic cells), anti-CD80, anti-CD86, anti-CD40, anti-MHCII, anti-CD8a, anti-CD4, and anti-CD103. Other markers that may be analyzed include pan-immune cell marker CD45, T cell markers (CD3, CD4, CD8, CD25, Foxp3, T-bet, Gata3, Rorγ-t, Granzyme B, CD69, PD-1, CTLA-4), and macrophage/myeloid markers (CD11b, MHCII, CD206, CD40, CSF1R, PD-L1, Gr-1, F4/80). In addition to immunophenotyping, serum cytokines can be analyzed including, but not limited to, TNFα, IL-17, IL-13, IL-12p70, IL12p40, IL-10, IL-6, IL-5, IL-4, IL-2, IL-1b, IFNγ, GM-CSF, G-CSF, M-CSF, MIG, IP10, MIP1b, RANTES, and MCP-1. Cytokine analysis may be carried out on immune cells obtained from lymph nodes or other tissue, and/or on purified CD45⁺ infiltrated immune cells obtained ex vivo. Finally, immunohistochemistry is carried out on various tissue sections to measure T cells, macrophages, dendritic cells, and checkpoint molecule protein expression.

[1853] Ears may be removed from the sacrificed animals and placed in cold EDTA-free protease inhibitor cocktail (Roche). Ears are homogenized using bead disruption and supernatants analyzed for various cytokines by Luminex kit (EMD Millipore) as per manufacturer's instructions. In addition, cervical lymph nodes are dissociated through a cell

strainer, washed, and stained for FoxP3 (PE-FJK-16s) and CD25 (FITC-PC61.5) using methods known in the art.

[1854] In order to examine the impact and longevity of DTH protection, rather than being sacrificed, some mice may be rechallenged with the challenging antigen at a later time and mice analyzed for susceptibility to DTH and severity of response.

Example 7: Oral Administration

[1855] A subject can self-administer a solid dosage form orally in the morning with water, refraining from consuming acidic drinks 1 hour either side of dosing and from eating 2 hours before dosing and 1 hour after dosing.

Incorporation by Reference

[1856] All publications patent applications mentioned herein are hereby incorporated by reference in their entirety as if each individual publication 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

[1857] 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.

We claim:

1. A solid dosage form comprising a pharmaceutical agent, wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), and wherein the solid dosage form is enterically coated.
2. The solid dose form of claim 1, wherein the solid dose form is for oral administration and/or for therapeutic use.
3. The solid dose form of claim 1 or claim 2 comprising a therapeutically effective amount of the pharmaceutical agent.
4. The solid dosage form of any one of claims 1 to 3, wherein the solid dosage form comprises a capsule.
5. The solid dosage form of claim 4, wherein the enterically coated capsule is a size 00, size 0, size 1, size 2, size 3, size 4, or size 5 capsule.
6. The solid dosage form of claim 1, wherein the solid dosage form comprises an enterically coated tablet.
7. The solid dosage form of claim 6, wherein the enterically coated tablet is a 5mm, 6mm, 7mm, 8mm, 9mm, 10mm, 11mm, 12mm, 13mm, 14mm, 15mm, 16mm, 17mm, or 18mm tablet.
8. The solid dosage form of claim 1, wherein the solid dosage form comprises a minitabket.
9. The solid dosage form of claim 8, wherein the minitabket is a 1mm minitabket, 1.5 mm minitabket, 2mm minitabket, 3mm minitabket, or 4mm minitabket.
10. The solid dosage form of claim 8 or 9, wherein a plurality of minitabkets are contained in a capsule.
11. The solid dosage form of claim 10, wherein the capsule is a size 00, size 0, size 1, size 2, size 3, size 4, or size 5 capsule.
12. The solid dosage form of claim 11, wherein the capsule is a size 0 capsule.
13. The solid dosage form of claim 12, wherein the size 0 capsule comprises 31-35 minitabkets.
14. The solid dosage form of claim 13, wherein the capsule comprises about 33 minitabkets.

15. The solid dosage form of any one of claims 8 to 14, wherein the minitablets are 3mm minitablets.
16. The solid dosage form of any one of claims 8 to 15, wherein the capsule comprises HPMC (hydroxyl propyl methyl cellulose) or gelatin.
17. The solid dosage form of any one of claims 1 to 6, wherein the enteric coating comprises one enteric coating.
18. The solid dosage form of any one of claims 1 to 17, wherein the enteric coating comprises an inner enteric coating and an outer enteric coating, and wherein the inner and outer enteric coatings do not contain identical components in identical amounts.
19. The solid dosage form of claim any one of claims 1 to 18, wherein the enteric coating comprises a methacrylic acid ethyl acrylate (MAE) copolymer (1:1).
20. The solid dosage form of claim any one of claims 1 to 19, wherein the enteric coating comprises one enteric coating which comprises a methacrylic acid ethyl acrylate (MAE) copolymer (1:1).
21. The solid dosage form of any one of claims 1 to 20, wherein the enteric coating comprises cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), poly(vinyl acetate phthalate) (PVAP), hydroxypropyl methylcellulose phthalate (HPMCP), a fatty acid, a wax, shellac (esters of aleurtic acid), a plastic, a plant fiber, zein, Aqua-Zein (an aqueous zein formulation containing no alcohol), amylose starch, a starch derivative, a dextrin, a methyl acrylate-methacrylic acid copolymer, cellulose acetate succinate, hydroxypropyl methyl cellulose acetate succinate (hypromellose acetate succinate), a methyl methacrylate-methacrylic acid copolymer, or sodium alginate.
22. The solid dosage form of any one of claims 1 to 21, wherein the enteric coating comprises an anionic polymeric material.
23. The solid dosage form of any one of claims 1 to 22, wherein the pharmaceutical agent comprises bacteria.
24. The solid dosage form of any one of claims 1 to 23, wherein the pharmaceutical agent comprises microbial extracellular vesicles (mEV).
25. The solid dosage form of any one of claims 1 to 24, wherein the pharmaceutical agent comprises isolated bacteria.

26. The solid dosage form of any one of claims 23 to 25, wherein at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% of the content of the pharmaceutical agent is the bacteria.
27. The solid dosage form of any one of claims 23 to 26, wherein the bacteria comprise bacteria that have been gamma irradiated, UV irradiated, heat inactivated, acid treated, or oxygen sparged.
28. The solid dosage form of any one of claims 23 to 27, wherein the bacteria comprise live bacteria.
29. The solid dosage form of any one of claims 23 to 28, wherein the bacteria comprise dead bacteria.
30. The solid dosage form of any one of claims 23 to 29, wherein the bacteria comprise non-replicating bacteria.
31. The solid dosage form of any one of claims 23 to 30, wherein the bacteria are from one strain of bacteria.
32. The solid dosage form of any one of claims 23 to 31, wherein the bacteria are lyophilized.
33. The solid dosage form of claim 32, wherein the lyophilized bacteria are in admixture with a pharmaceutically acceptable excipient.
34. The solid dosage form of any one of claims 23 to 33, wherein the bacteria are gamma irradiated.
35. The solid dosage form of any one of claims 23 to 34, wherein the bacteria are UV irradiated.
36. The solid dosage form of any one of claims 23 to 35, wherein the bacteria are heat inactivated.
37. The solid dosage form of claim 36, wherein the bacteria are heat inactivated at about 50°C for at least two hours or at about 90°C for at least two hours.
38. The solid dosage form of any one of claims 23 to 37, wherein the bacteria are acid treated.
39. The solid dosage form of any one of claims 23 to 38, wherein the bacteria are oxygen sparged.

40. The solid dosage form of claim 39, wherein the bacteria are oxygen sparged at 0.1 vvm for two hours.
41. The solid dosage form of any one of claims 23 to 40, wherein the bacteria are Gram positive bacteria.
42. The solid dosage form of any one of claims 23 to 40, wherein the bacteria are Gram negative bacteria.
43. The solid dosage form of any one of claims 23 to 42, wherein the bacteria are aerobic bacteria.
44. The solid dosage form of any one of claims 23 to 42, wherein the bacteria are anaerobic bacteria.
45. The solid dosage form of any one of claims 23 to 44, wherein the bacteria are acidophile bacteria.
46. The solid dosage form of any one of claims 23 to 44, wherein the bacteria are alkaliphile bacteria.
47. The solid dosage form of any one of claims 23 to 44, wherein the bacteria are neutralophile bacteria.
48. The solid dosage form of any one of claims 23 to 47, wherein the bacteria are fastidious bacteria.
49. The solid dosage form of any one of claims 23 to 47, wherein the bacteria are nonfastidious bacteria.
50. The solid dosage form of any one of claims 23 to 49, wherein the bacteria are from a class, order, family, genus, species and/or strain listed in Table 1, Table 2, or Table 3.
51. The solid dosage form of claim 50, wherein the bacteria are from a bacterial strain listed in Table 1, Table 2, or Table 3.
52. The solid dosage form of any one of claims 23 to 51, wherein the bacteria are from bacteria from a class, order, family, genus, species and/or strain listed in Table J.
53. The solid dosage form of claim 52, wherein the bacteria are from a bacterial strain listed in Table J.

54. The solid dosage form of any one of claims 1 to 22, wherein the pharmaceutical agent comprises isolated mEVs.

55. The solid dosage form of claim 54 comprising a therapeutically effective amount of the isolated mEVs.

56. The solid dosage form of claim 54 or 55, wherein at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% of the content of the pharmaceutical agent is the isolated mEVs.

57. The solid dosage form of any one of claims 54 to 56, wherein the mEVs comprise secreted mEVs (smEVs).

58. The solid dosage form of any one of claims 54 to 57, wherein the mEVs comprise processed mEVs (pmEVs).

59. The solid dosage form of claim 58, wherein the pmEVs are produced from bacteria that have been gamma irradiated, UV irradiated, heat inactivated, acid treated, or oxygen sparged.

60. The solid dosage form of claims 58 or 59, wherein the pmEVs are produced from live bacteria.

61. The solid dosage form of claims 58 or 59, wherein the pmEVs are produced from dead bacteria.

62. The solid dosage form of claims 58 or 59, wherein the pmEVs are produced from non-replicating bacteria.

63. The solid dosage form of any one of claims 54 to 62, wherein the mEVs are from one strain of bacteria.

64. The solid dosage form of any one of claims 54 to 63, wherein the mEVs are lyophilized.

65. The solid dosage form of claim 64, wherein the lyophilized mEVs are in admixture with a pharmaceutically acceptable excipient).

66. The solid dosage form of any one of claims 54 to 65, wherein the mEVs are gamma irradiated.

67. The solid dosage form of any one of claims 54 to 66, wherein the mEVs are UV irradiated.

68. The solid dosage form of any one of claims 54 to 67, wherein the mEVs are heat inactivated.
69. The solid dosage form of claim 68, wherein the mEVs are heat inactivated at about 50°C for at least two hours or at about 90°C for at least two hours.
70. The solid dosage form of any one of claims 54 to 69, wherein the mEVs are acid treated.
71. The solid dosage form of any one of claims 54 to 70, wherein the mEVs are oxygen sparged.
72. The solid dosage form of claim 71, wherein the mEVs are oxygen sparged at 0.1 vvm for two hours.
73. The solid dosage form of any one of claims 54 to 72, wherein the mEVs are from Gram positive bacteria.
74. The solid dosage form of any one of claims 54 to 72, wherein the mEVs are from Gram negative bacteria.
75. The solid dosage form of any one of claims 45 to 74, wherein the mEVs are from aerobic bacteria.
76. The solid dosage form of any one of claims 54 to 74, wherein the mEVs are from anaerobic bacteria.
77. The solid dosage form of any one of claims 54 to 76, wherein the mEVs are from acidophile bacteria.
78. The solid dosage form of any one of claims 54 to 76, wherein the mEVs are from alkaliphile bacteria.
79. The solid dosage form of any one of claims 54 to 76, wherein the mEVs are from neutralophile bacteria.
80. The solid dosage form of any one of claims 54 to 79, wherein the mEVs are from fastidious bacteria.
81. The solid dosage form of any one of claims 54 to 79, wherein the mEVs are from nonfastidious bacteria.

82. The solid dosage form of any one of claims 54 to 81, wherein the mEVs are from bacteria of a class, order, family, genus, species and/or strain listed in Table 1, Table 2, or Table 3.
83. The solid dosage form claim 82, wherein the mEVs are from a bacterial strain listed in Table 1, Table 2, or Table 3.
84. The solid dosage form of any one of claims 54 to 83, wherein the mEVs are from bacteria of a class, order, family, genus, species and/or strain listed in Table J.
85. The solid dosage form of claim 84, wherein the mEVs are from a bacterial strain listed in Table J.
86. The solid dosage form of any one of claims 23 to 53, wherein the dose of bacteria is about 1×10^7 to about 2×10^{12} cells, wherein the dose is per capsule or tablet or per total number of minitabets in a capsule.
87. The solid dosage form of claim 86, wherein the dose of bacteria is about 3×10^{10} or about 1.5×10^{11} or about 1.5×10^{12} .
88. The solid dosage form of claim 86, wherein the pharmaceutical agent comprises bacteria and the dose of bacteria is about 1×10^9 , about 3×10^9 , about 5×10^9 , about 1.5×10^{10} , about 3×10^{10} , about 5×10^{10} , about 1.5×10^{11} , about 1.5×10^{12} , or about 2×10^{12} cells, wherein the dose is per capsule or tablet or per total number of minitabets in a capsule.
89. The solid dosage form of any one of claims 1 to 88, wherein the dose of the pharmaceutical agent is about 10 mg to about 1500 mg, wherein the dose is per capsule or tablet or per total number of minitabets in a capsule.
90. The solid dosage form of any one of claims 1 to 88, wherein the dose of the pharmaceutical agent is about 30 mg to about 1300 mg by weight, wherein the dose is per capsule or tablet or per total number of minitabets in a capsule.
91. The solid dosage form of claim 90, wherein the dose is about 25, about 30, about 35, about 50, about 75, about 100, about 120, about 150, about 250, about 300, about 350, about 400, about 500, about 600, about 700, about 750, about 800, about 900, about 1000, about 1100, about 1200, about 1250, about 1300, about 2000, about 2500, about 3000, or about 3500 mg, wherein the dose is per capsule or tablet or per total number of minitabets in a capsule

92. The solid dosage form of any one of claims 1 to 88, wherein the dose of the pharmaceutical agent is about 2×10^6 to about 2×10^{16} particles, wherein the dose is per capsule or tablet or per total number of minitabets in a capsule.
93. The solid dosage form of claim 92, wherein particle count is determined by nanoparticle tracking analysis (NTA).
94. The solid dosage form of any one of claims 1 to 88, wherein the dose of the pharmaceutical agent is about 5 mg to about 900 mg total protein, wherein the dose is per capsule or tablet or per total number of minitabets in a capsule.
95. The solid dosage form of claim 94, wherein total protein is determined by Bradford assay or by BCA.
96. The solid dosage form of any one of claims 1 to 95, wherein the solid dosage form further comprises one or more additional pharmaceutical agents.
97. The solid dosage form of any one of claims 1 to 96, wherein the solid dosage form further comprises an excipient.
98. The solid dosage form of claim 97, wherein the excipient is a diluent, a binder and/or an adhesive, a disintegrant, a lubricant and/or a glidant, a coloring agent, a flavoring agent, and/or a sweetening agent.
99. A method of treating a subject, the method comprising administering to the subject a solid dosage form of any one of claims 1 to 98.
100. The solid dosage form of any one of claims 1 to 98 for use in treating a subject.
101. Use of a solid dosage form of any one of claims 1 to 98 for the preparation of a medicament for treating a subject.
102. The method, solid dosage form, or use of any one of claims 99 to 101, wherein the solid dosage form is orally administered.
103. The method, solid dosage form, or use of any one of claims 99 to 102, wherein the solid dosage form is administered on an empty stomach.
104. The method, solid dosage form, or use of any one of claims 99 to 103, wherein the solid dosage form is administered 1, 2, 3, or 4 times a day.

105. The method, solid dosage form, or use of any one of claims 99 to 104, wherein the solid dosage form comprises a tablet or a plurality of minitabets within a capsule, and 1, 2, 3, or 4 solid dosage forms are administered 1, 2, 3, or 4 times a day.
106. The method, solid dosage form, or use of any one of claims 99 to 105, wherein the subject is in need of treatment and/or prevention of a cancer.
107. The method, solid dosage form, or use of any one of claims 99 to 105, wherein the subject is in need of treatment and/or prevention of an autoimmune disease.
108. The method, solid dosage form, or use of any one of claims 99 to 105, wherein the subject is in need of treatment and/or prevention of an inflammatory disease.
109. The method, solid dosage form, or use of any one of claims 99 to 105, wherein the subject is in need of treatment and/or prevention of a metabolic disease.
110. The method, solid dosage form, or use of any one of claims 99 to 105, wherein the subject is in need of treatment and/or prevention of dysbiosis.
111. The method, solid dosage form, or use of any one of claims 99 to 110, wherein the solid dosage form is administered in combination with an additional pharmaceutical agent.
112. A method for preparing an enterically coated capsule comprising a pharmaceutical agent, wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), the method comprising:
- a) combining the pharmaceutical agent with a pharmaceutically acceptable excipient;
 - b) loading the pharmaceutical agent and pharmaceutically acceptable excipient into a capsule; and
 - c) enterically coating the capsule, thereby preparing the enterically coated capsule.
113. The method of claim 112, wherein the method comprises combining the pharmaceutical agent with a pharmaceutically acceptable excipient prior to loading into the capsule.
114. The method of claim 112, wherein the method comprises banding the capsule after loading the capsule and prior to enterically coating the capsule.

115. A method for preparing an enterically coated tablet comprising a pharmaceutical agent, wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), the method comprising:

- a) combining the pharmaceutical agent with a pharmaceutically acceptable excipient;
- b) compressing the pharmaceutical agent and pharmaceutically acceptable excipient, thereby forming a tablet; and
- c) enterically coating the tablet, thereby preparing an enterically coated tablet.

116. A method for preparing an enterically coated minitabket comprising a pharmaceutical agent, wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), the method comprising:

- a) combining the pharmaceutical agent with a pharmaceutically acceptable excipient;
- b) compressing the pharmaceutical agent and pharmaceutically acceptable excipient, thereby forming a minitabket; and
- c) enterically coating the minitabket, thereby preparing the enterically coated minitabket.

117. The method of claim 116, wherein the minitabket is loaded into a capsule.

118. A method for preparing a capsule comprising enterically coated minitabkets comprising a pharmaceutical agent, wherein the pharmaceutical agent comprises bacteria and/or microbial extracellular vesicles (mEVs), the method comprising:

- a) combining the pharmaceutical agent with a pharmaceutically acceptable excipient;
- b) compressing the pharmaceutical agent and pharmaceutically acceptable excipient, thereby forming a minitabket;
- c) enterically coating the minitabket, thereby preparing an enterically coated minitabket, and
- d) loading the capsule with one or more enterically coated minitabkets, thereby preparing the capsule.

119. The method of any one of claims 112 to 118, wherein the pharmaceutical agent comprises a therapeutically effective amount of bacteria and/or mEVs.

Figure 1

