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(57) Abstract: The present invention relates to pharmaceutical compositions and methods suitable for the treatment of intestinal disorders and chronic diseases associated with the presence of abnormal distribution of microflora in the gastrointestinal tract of a mammalian host. Furthermore, the present invention relates to pharmaceutical compositions methods suitable for the treatment intestinal disorders and chronic diseases, including but not limited to bacterial infection, irritable bowel syndrome (IBS) or spastic colon, idiopathic ulcerative colitis, mucous colitis, collagenous colitis, Crohn's disease, inflammatory bowel disease, antibiotic-associated colitis, gastrointestinal cancer, and idiopathic or simple constipation and insulin resistance. Moreover, the present invention relates to kits suitable for the treatment of intestinal disorders and chronic diseases associated with the presence of abnormal or an abnormal distribution of microflora in the gastrointestinal tract of a mammalian host.

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RAPID RECOLONIZATION DEPLOYMENT AGENT

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority to United States Provisional Patent Application Serial No. 61/475,865 filed 15 April 2011, which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions and methods suitable for the treatment of intestinal disorders and chronic diseases associated with the presence of abnormal distribution of microflora in the gastrointestinal tract of a mammalian host.

BACKGROUND

All publications herein are incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference. The following description includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

There are a large number of gastro-intestinal diseases that can be, at least in part, attributable to an imbalance, disruption, or abnormal distribution of microflora in the gastrointestinal tract of a mammalian host. These diseases include, but are not limited to, Clostridium difficile-associated diarrhea and colitis, insulin resistance, irritable bowel syndrome (IBS) or spastic colon, idiopathic ulcerative colitis, mucous colitis, collagenous colitis, Crohn's disease, inflammatory bowel disease in general, microscopic colitis, antibiotic-associated colitis, and idiopathic or simple constipation. Over the past few decades, several researchers have begun treating several of these diseases using a form of probiotics called fecal bacteriotherapy or fecal transfusion/transplant to help re-establish and/or rebalance the gut flora. (For a review see Borody, T.J. et al., "Bacteriotherapy using fecal flora: toying with human motions," J Clin Gastroenterol, 38: 475-83, 2004; McFarland, L. V. "Evidence-Based Review of Probiotics for Antibiotic-Associated Diarrhea." Anaerobe, 2009;15:271-280; Quigley, E. M. M. "Probiotics in Gastrointestinal Disorders." Hospital Practice. 2010;38:15 pages.) In general, these researchers have met with great success.
Recent studies have demonstrated that certain gut species are more prevalent or more conserved between individuals, thus constituting a phylogenetic core of gut flora. (Tap, J. et al., "Towards the human intestinal microbiota phylogenetic core," Environmental Microbiology, 11:2574-2584, 2009; which is hereby incorporated by reference in its entirety and especially for its teachings related to the phylogenetic core). This phylogenetic core of gut flora has been reported to include Faecalibacterium prausnitzii, Eubacterium rectale, Ruminococcus bromii, Alistipes putredinis, Subdoligranulum sp, Bacteroides vulgatus, Bacteroides uniformis rel, Parabacteroides distasonis, Bifidobacterium longum, Dorea formicigenerans, and Roseburia intestinalis. Tap et al., further reported that the phylogenetic core constituted bacteria from the phyla Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria and Verruromicrobia, in the proportions of 79.4%, 16.9%, 2.5%, 1%. and 0.1%, respectively.

Fecal bacteriotherapy uses the complete normal human flora as a therapeutic probiotic mixture of living organisms. This type of bacteriotherapy has a longstanding history in animal health and has been used sporadically against chronic infections of the bowel. It involves infusion of bacterial flora acquired from the feces of a healthy donor to reverse the bacterial imbalance responsible for the recurring nature of the infection.

Although fecal bacteriotherapy has had significant clinical success in treating gastrointestinal diseases, it has not been embraced by patients as a viable option. This is believed to be at least partly due to the thought of using a treatment where fecal matter is transplanted into the intestinal tract of a patient, wherein the fecal matter may or may not be from self. Furthermore, although all of the fecal bacteriotherapy treatments screen for potential infectious or opportunistic microorganisms, errors occur and there have been a number of situations where a further infection was caused by the treatment, fecal bacteriotherapy. Moreover, a disadvantage of many of the fecal bacteriotherapy formulations is the poor shelf life of the formulations.

Therefore, a significant need exists in the art for improvements to fecal bacteriotherapy, wherein patients will readily choose this sort of treatment as a viable option. This is because fecal matter is not being transfused, transferred, or transplanted into their intestinal tract, and the treatment comprises a predetermined set of gut flora that do not include any potential infectious or opportunistic microorganisms. Moreover, there is a need in the art for the treatment to have improved stability and increased delivery of viable gut flora. In particular, a need exists for providing stable gut flora compositions comprising
bacterial strains that have previously been very difficult to store long-term or at room temperature.

**SUMMARY OF THE INVENTION**

The following embodiments and aspects thereof are described and illustrated in conjunction with compositions and methods which are meant to be exemplary and illustrative, not limiting in scope.

The present invention provides for a pharmaceutical composition comprising a pre-selected combination of microorganisms useful in the treatment of intestinal disorders, conditions, or disease.

In various embodiments, the intestinal disorders include a bacterial infection, irritable bowel syndrome (IBS) or spastic colon, idiopathic ulcerative colitis, mucous colitis, collagenous colitis, Crohn's disease, inflammatory bowel disease, antibiotic-associated colitis, gastrointestinal cancer, and idiopathic or simple constipation or wherein the bacterial infection is at least one of *H. pylori*, *Salmonella*, *Shigella*, *Staphylococcus*, *Campylobacter*, *Clostridium*, *Escherichia coli*, *Yersinia*, and *Vibrio*. In further embodiments, the gastrointestinal cancer is at least one of stomach cancer, esophageal cancer, colon cancer gallbladder cancer, liver cancer, pancreatic cancer, colorectal cancer, anal cancer, and gastrointestinal stromal tumors.

In further embodiments, the pharmaceutical composition, wherein there is a pre-selected combination of microorganisms, includes at least one of *Faecalibacterium prausnitzii*, *Eubacterium rectale*, *Ruminococcus bromii*, *Alistipes putredinis*, *Subdoligranulum sp.*, *Bacteroides vulgatus*, *Bacteroides uniformis rel*, *Parabacteroides distasonis*, *Dorea formicigenerans*, *Roseburia intestinalis*, *Coprobacillus sp.*., *Anaerostipes caccae*, *Clostridium spiroforme*, *Dorea longicatena*, *Clostridium sp. BI-114*, *Clostridium bolteae*, *Eubacterium halii*, *Eubacterium eligens*, *Ruminococcus obeum*, *Alistipes shahii*, *Bacteroides stercoris*, and *Bacteroides massiliensis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Lactobacillus zeae*, *Lactobacillus salivarius*, *Lactobacillus lactis*, *Lactobacillus helveticus*, *Lactobacillus reuteri*, *Lactobacillus amylovorus*, *Lactobacillus crispatus*, *Lactobacillus curvatus*, *Lactobacillus delbrueckii*, *Lactobacillus gasseri*, *Lactobacillus johnsonii*, *Streptococcus thermophilus*, *Lactobacillus bulgaricus*, *Lactobacillus fermentum*, *Lactobacillus brevis*, *Lactococcus lactis*, *Lactococcus cremoris*, *Leuconostoc spp.*; *Enterococcus faecium*, *Prevotella species*, *Methanobrevibacter species* (e.g. *M. acididurans*, *M. arboriphilus*, *M. curvatus*, *M. cuticularis*, *M. filiformis*, *M.
gottschalkii, M. millerae, M. olleyae, M. oralis, M. ruminantium, M. smithii, M. thaueri, M. woeaei, M. wolini), Pediococcus pentosaceus, Pediococcus acidilactici, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium bifidum, Bifidobacterium infantis, Bifidobacterium lactis, Blautia hansenii, Clostridium scindens, Enterococcus faecalis TX0104, Clostridium asparagiforme, Bacteroides fragilis 3_1_12, Bacteroides intestinalis, Ruminococcus gnavus, Anaerotruncus colihominis, Bacteroides pectinophilus, Clostridium nexile, Clostridium coccoideis, Clostridium sp. L2-50, Parabacteroides johnsonii, Bacteroides finegoldii, Butyrvibrio crosstus, Bacteroides eggerthii, Clostridium sp. M62 1, Coprococcus eutactus, Holdemania filiformis, Clostridium leptum, Streptococcus thermophilus LMD-9, Bacteroides capillosus, Bacteroides dorei, Eubacterium ventriosum, Bacteroides sp. D4, Bacteroides sp. Dl, Coprococcus comes SL7 1. Bacteroides xylanisolvens XB1A, Bacteroides sp. 2_2_4, Bacteroides sp. 4_3_47FAA, Bacteroides ovatus, Bacteroides sp. 9_1_42FAA, Eubacterium siraeum 70 3, Bacteroides sp. 2_1_7, Collinsella aerofaciens, Ruminococcus lactaris, Ruminococcus sp. SRI 5, Unknown sp. SS3 4, Ruminococcus torques L2-14, Bacteroides thetaiotaomicron VPI-5482, Clostridium sp. SS2-1, Bacteroides caccae, Parabacteroides merdae, and propionibacterial species, yeast species and mold species. In further embodiments, the pharmaceutical composition further comprises the combination of microorganisms contained within at least one of a capsule, suppository, device, and enema. In still further embodiments, the pharmaceutical composition further comprises a composition capable of having a prolonged shelf-life.

In various embodiments, the pharmaceutical composition comprising a pre-selected combination of microorganism is useful in a supportive therapeutic treatment.

The present invention also provides a method of treating an intestinal disorder or symptom thereof, comprising: providing a composition capable of reestablishing the intestinal flora; and administering a therapeutically effective amount of the composition to a subject in need thereof. The present invention also provides a method of treating an insulin resistance or symptom thereof, comprising: providing a composition capable of reestablishing the intestinal flora; and administering a therapeutically effective amount of the composition to a subject in need thereof.

The present invention also provides for a kit for the treatment of an intestinal disorder or symptom thereof; comprising: an agent selected from the group consisting of: Faecalibacterium prausnitzii, Eubacterium rectale, Ruminococcus bromii, Alistipes putredinis, Subdoligranulum sp, Bacteroides vulgatus, Bacteroides uniformis rel, Parabacteroides distasonis, Dorea formicigenerans, Roseburia intestinalis, Coprobacillus
sp., Anaerostipes caccae, Clostridium spiroforme, Dorea longicatena, Clostridium sp. Bi-114, Clostridium bolteae, Eubacterium halii, Eubacterium eligens, Ruminococcus obeum, Alistipes shahii, Bacteroides stercoris, and Bacteroides massiliensis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus rhamnosus, Lactobacillus zeae, Lactobacillus salivarius, Lactobacillus lactis, Lactobacillus helvicicus, Lactobacillus reuteri, Lactobacillus amylovorus, Lactobacillus crispatus, Lactobacillus curvatus, Lactobacillus delbrueckii, Lactobacillus gasseri, Lactobacillus johnsonii, Streptococcus thermophilus, Lactobacillus bulgaricus, Lactobacillus fermentum, Lactobacillus brevis, Lactococcus lactis, Lactococcus cremoris, Leuconostoc spp.; Entercoccus faecium, Prevotella species, Methanobrevibacter species (e.g. M. acididurans, M. arboriphilus, M. curvatus, M. cuticularis, M. filiformis, M. gottschalkii, M. millerae, M.olleyae, M. oralis, M. ruminantium, M. smithii, M. thaueri, M. woesei, M. wolinii), Pediococcus pentosaceus, Pediococcus acidilactici, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium bifidum, Bifidobacterium infantis, Bifidobacterium lactis, Blautia hansenii, Clostridium scindens, Enterococcus faecalis TX0104, Clostridium asparagiforme, Bacteroides fragilis 3_1_12, Bacteroides intestinalis, Ruminococcus gnavus, Anaerotruncus colihominis, Bacteroides pectinophilus, Clostridium nexile, Clostridium cocoides, Clostridium sp. L2-50, Parabacteroides johnsonii, Bacteroides finegoldii, Butyrivibrio crosotus, Bacteroides eggerthii, Clostridium sp. M62 1, Coprococcus eutactus, Holdemania filiformis, Clostridium leptum, Streptococcus thermophilus LMD-9, Bacteroides capillosus, Bacteroides dorei, Eubacterium ventriosum, Bacteroides sp. D4, Bacteroides sp. Dl, Coprococcus comes SL7 1, Bacteroides xylanisolvens XB1A, Bacteroides sp. 2^2_4, Bacteroides sp. 4_3_47FAA, Bacteroides ovatus, Bacteroides sp. 9_1_42FAA, Eubacterium siraeum 70 3, Bacteroides sp. 2_1_7, Collinsella aerofaciens, Ruminococcus lactaris, Ruminococcus sp. SRI 5, Unknown sp. SS3 4, Ruminococcus torques L2-14, Bacteroides thetaitaomaicron VPI-5482, Clostridium sp. SS2-1, Bacteroides caccae, Parabacteroides merdae, and propionibacterial species, yeast species and mold species; a composition capable of prolonged shelf-life; and instructions to use the agent to treat the intestinal disorder or symptom thereof.

Other features and advantages of the invention will become apparent from the following detailed description, which illustrate, by way of example, various features of embodiments of the invention.
BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the microbes and the relative frequencies of the microbes that can be utilized in the rapid recolonization deployment agent.

DETAILED DESCRIPTION OF THE INVENTION

Certain embodiments disclosed herein relate to pharmaceutical compositions and methods of treatment, wherein the rapid recolonization of normal gut flora in a compromised intestinal tract is stimulated through introduction of microbial components and associated environmental modifiers that mimic those found in a normal, healthy individual. Through this introduction, normal (and even superior) intestinal health is restored and opportunistic infectious agents (e.g. Clostridium difficile, Vibrio cholerae, and species of Campylobacter) are suppressed. Further embodiments disclosed herein relate to novel pharmaceutical compositions suitable for the treatment of various disease states related to the presence of "abnormal" microflora in the gastrointestinal tract.

Certain embodiments disclosed herein relate to pharmaceutical compositions, devices and methods of treatment, involving a reconstitution of gut flora from healthy individuals, including the appropriate proportions of each individual microorganism. To that end, the microbial and other components used in the compositions, devices and methods may, in certain embodiments, be substantially similar to that which one would find in fecal matter used in fecal transplant procedures.

Further embodiments disclosed herein, relate to pharmaceutical compositions and methods of treatment, wherein the patients will readily choose this sort of treatment (rapid recolonization deployment agent) as a viable option. This is because fecal matter is not being transfused, transferred, or transplanted into their intestinal tract, and the treatment comprises a predetermined set of gut flora that do not include any potential infectious or opportunistic microorganisms.

According to certain embodiments, the inventive rapid recolonization deployment agent can substitute for fecal transfusion and can contain cleaner, more stabilized, and more accurate intestinal and/or gut flora to help in re-establishing proper intestinal and/or gut flora.

According to certain embodiments, the rapid recolonization deployment agent can include microbial agents and associated elements in a shelf-stable form produced by culture and stabilized via freeze-dry process. According to further embodiments, upon use, the agent is rehydrated in sterile water and introduced through direct access to colon (enema, suppository, or capsule insertion).
Certain embodiments herein relate to therapeutic compositions and methods of treatment for a subject by preventing or alleviating at least one symptom of a digestive associated condition or disease. For example, the therapeutic compositions and/or methods disclosed herein may be useful for treating or preventing one or more condition or disease selected from the group consisting of gastritis, peptic ulcer, duodenal ulcer, gastroesophageal reflux disease (GERD), acid reflux, eosinophilic esophagitis, inflammatory bowel disease (such as Crohn's disease), gastrointestinal cancer (e.g., stomach cancer, esophageal cancer, colon cancer gallbladder cancer, liver cancer, pancreatic cancer, colorectal cancer, anal cancer, and gastrointestinal stromal tumors), irritable bowel syndrome, infection or trauma to the gastrointestinal tract, including infection by *H. pylori, Salmonella, Shigella, Staphylococcus, Campylobacter, Clostridium, Escherichia coli, Yersinia, Vibrio, Candida, Giardia, Entamoeba histolytica*, rotavirus, norovirus, adenovirus and astrovirus, inflammation in the gastrointestinal tract, ulcerative colitis, and others.

Symptoms of digestive conditions or disorders generally include pain, nausea, vomiting, diarrhea, dysentery, constipation, bloating, sore throat, laryngeal or respiratory irritation, oropharyngeal irritation, weight loss or weight gain, and the like.

According to certain embodiments, the rapid recolonization deployment agent can be used to suppress opportunistic intestinal infections (e.g., *Vibrio cholerae, Campylobacter*). According to further embodiments, the rapid recolonization deployment agent can be used as prophylactic support of gut flora during heavy antibiotic regimens or other therapies hostile to normal gut flora. According to still further embodiments, the rapid recolonization deployment agent can be used to reestablish normal gut performance in inflammatory processes or acute injury.

According to further embodiments, the rapid recolonization deployment agent can contain microbial agents and associated environmental and promotional elements. According to still further embodiments, the inventive rapid recolonization deployment agents are produced in a shelf-stabilized and/or room temperature stabilized formulation. This shelf-stabilized and/or room temperature stabilized formulation can be via freeze-drying.

According to still further embodiments, the rapid recolonization deployment agent can be introduced via direct access to the compromised gut (tube, enema, suppository or similar mechanism). According to certain embodiments, upon introduction of these microbial agents, viable colonies are re-established within the gut, displacing the opportunistic infectious agent(s). Importantly, this method of action has already been shown as a viable treatment option via direct fecal transplant procedures. According to particular
aspects, the rapid recolonization deployment agent can be optimized to determine the most appropriate composition of microorganisms. In particular aspects, composition of microorganisms contained in the rapid recolonization deployment agent can be different combinations of intestinal flora. In further particular aspects, gut flora that can be useful in the current invention (rapid recolonization deployment agent) include, but are not limited to, Faecalibacterium prausnitzii, Eubacterium rectale, Ruminococcus bromii, Alistipes putredinis, Subdoligranulum sp, Bacteroides vulgatus, Bacteroides uniformis rel, Parabacteroides distasonis, Dorea formicigenerans, Roseburia intestinalis, Coprobacillus sp., Anaerostipes caccae, Clostridium spiroforme, Dorea longicatena, Clostridium sp. BI-114. Clostridium bolteae, Eubacterium halii, Eubacterium eligens, Ruminococcus obeum, Alistipes shahii, Bacteroides stercoris, and Bacteroides massiliensis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus rhamnosus, Lactobacillus zeae, Lactobacillus salivarius, Lactobacillus lactis, Lactobacillus helveticus, Lactobacillus reuteri, Lactobacillus amylovorus, Lactobacillus crispatus, Lactobacillus curvatus, Lactobacillus delbrueckii, Lactobacillus gasseri, Lactobacillus johnsonii, Streptococcus thermophilus, Lactobacillus bulgaricus, Lactobacillus fermentum, Lactobacillus brevis, Lactococcus lactis, Lactococcus cremoris, Leuconostoc spp.; Enterococcus faecium, Prevotella species, Methanobrevibacter species (e.g. M. acidurans, M. arboriphilus, M. curvatus, M. cuticularis, M. filiformis, M. gottschalkii, M. millerae, M.olleyae, M. oralis, M. ruminantium, M. smithii, M. thaueri, M. woesei, M. wolinii), Pediococcus pentosaceus, Pediococcus acidilactici, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium bifidum, Bifidobacterium infantis, Bifidobacterium lactis, Blautia hansenii, Clostridium scindens, Enterococcus faecalis TX0104, Clostridium asparagiforme, Bacteroides fragilis 3_1_12, Bacteroides intestinalis, Ruminococcus gnavus, Anaerotruncus colihominis, Bacteroides pectinophilus, Clostridium nexile, Clostridium coccoidei, Clostridium sp. L2-50, Parabacteroides johnsonii, Bacteroides finegoldii, Butyrivibrio crosstus, Bacteroides eggerthii, Clostridium sp. M62 1. Coprococcus eutactus, Holdemania filiformis, Clostridium leptum, Streptococcus thermophilus LMD-9, Bacteroides capillosus, Bacteroides dorei, Eubacterium ventriosum, Bacteroides sp. D4, Bacteroides sp. DI, Coprococcus comes SL7 1, Bacteroides xylanisolvens XB1A, Bacteroides sp. 2_2_4, Bacteroides sp. 4_3_47FAA, Bacteroides ovatus, Bacteroides sp. 9_1_42FAA, Eubacterium siraeum 70 3, Bacteroides sp. 2_1_7, Collinsella aerofaciens, Ruminococcus lactaris, Ruminococcus sp. SRI 5, Unknown sp. SS3 4, Ruminococcus torques L2-14, Bacteroides thetaiotaomicron VPI-5482, Clostridium sp. SS2-1, Bacteroides caccae, Parabacteroides
merdae, and propionibacterial species, yeast species and mold species. In preferred aspects, gut flora that can be useful in the current invention (rapid recolonization deployment agent) includes Faecalibacterium prausnitzii. In other preferred aspects, gut flora that can be useful in the current invention (rapid recolonization deployment agent) includes at least one Methanobrevibacter. In further preferred aspects, gut flora that can be useful in the current invention (rapid recolonization deployment agent) includes M. smithii.

In certain embodiments, the rapid recolonization deployment agent can be optimized to include microorganisms from certain phyla in certain proportions. In preferred embodiments, the rapid recolonization deployment agent includes microorganisms from the Firmicutes, Bacteroidetes, Actinobacteria phyla, wherein the bacterial proportions of each are at least 25%, 5%, and 0.5%, respectively. In preferred embodiments, the rapid recolonization deployment agent includes microorganisms from the Firmicutes, Bacteroidetes, Actinobacteria phyla, wherein the bacterial proportions of each are at least 45%, 8%, and 1.2%, respectively. In preferred embodiments, the rapid recolonization deployment agent includes microorganisms from the Firmicutes, Bacteroidetes, Actinobacteria phyla, wherein the bacterial proportions of each are at least 75%, 15%, and 2%, respectively. In most preferred embodiments, the rapid recolonization deployment agent includes microorganisms from the Firmicutes phyla, wherein bacteria from the Firmicutes phyla constitutes at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, or at least 75%. In other preferred embodiments, the rapid recolonization deployment agent includes microorganisms from the Euryarchaeota phyla.

According to certain embodiments, Figure 1 shows the microbes and the relative frequencies of the microbes that can be utilized in the rapid recolonization deployment agent. This figure is taken from Qin J. et al., (2010) "A human gut microbial gene catalogue established by metagenomic sequencing." Nature 464, 59-65 which is hereby incorporated by reference in its entirety). Boxes denote the interquartile range (IQR) between the first and third quartiles (25th and 75th percentiles, respectively) and the line inside denotes the median. Whiskers denote the lowest and highest values within 1.5 times IQR from the first and third quartiles, respectively. Circles denote outliers beyond the whiskers.

According to further embodiments, the rapid recolonization deployment agent can be optimized to include certain specific microorganisms in certain proportions. According to still further embodiments, the rapid recolonization deployment agent can be optimized to include, but not limited to, Bacteroides uniformis, Alistipes putredinis, Parabacteroides
merdae, Dorea longicatena, Ruminococcus bromii L2-63, Ruminococcus lactaris, Faecalibacterium prausnitzii SL3 3, Ruminococcus sp. SRI 5, Unknown sp. SS3 4, Ruminococcus torques L2-14, Eubacterium hallii, Bacteroides thetaiotaomicron VPI-5482, Clostridium sp. SS2-1, Bacteroides caccae.

According to further embodiments, the rapid recolonization deployment agent can be optimized to include certain specific microorganisms in certain proportions for certain indications. For example and according to yet further embodiments, the rapid recolonization deployment agent can be optimized to re-establish normal gut flora by including Bacteroides uniformis, Alistipes putredinis, Parabacteroides merdae, Dorea longicatena, Ruminococcus bromii L2-63, Ruminococcus lactaris, Faecalibacterium prausnitzii SL3 3, Ruminococcus sp. SRI 5, Unknown sp. SS3 4, Ruminococcus torques L2-14, Eubacterium hallii, Bacteroides thetaiotaomicron VPI-5482, Clostridium sp. SS2-1, Bacteroides caccae as the microbes contained in the agent. According to even further embodiments, the rapid recolonization deployment agent can be altered to deliver specific individual microbes, depending on the need of the subject. For example, if the subject is lacking sufficient amounts of Parabacteroides merdae or Dorea longicatena, then the rapid recolonization deployment agent can include those microbes to reestablish the correct relative amounts of them. In certain embodiments, the rapid recolonization deployment agent is useful in a supportive therapeutic treatment. According to certain embodiments, many diseases, disorders, or conditions or treatments for diseases, disorders, or conditions destabilize the gut microbium balance and the supportive therapy is useful in preventing or treating this imbalance. Supportive therapy as used herein refers to the use of the rapid recolonization deployment agent to be implemented prior to, concurrently, or post treatment for any disease, disorder, or condition. Some diseases, disorders, or conditions can include, but are not limited to heart disease, cancer (e.g., liver, pancreatic, kidney), metabolic syndrome, diabetes, autoimmune diseases (e.g., lupus, rheumatoid arthritis), neurologic diseases (e.g., multiple sclerosis, Alzheimer disease, Parkinson disease), autism spectrum, all colitis diseases (e.g., Crohn's disease, inflammatory bowel syndrome), acute bacterial infections, injuries and acute trauma, wherein the supportive therapy supports increased nutritional needs and immune function important for healing, behavioral and mental health (e.g., depression, ADHD, psychoses), allergies, and viral infections. In preferred embodiments, the rapid recolonization deployment agent is useful in supportive therapeutic treatment of cancers, heart disease, and autoimmune disease. According to certain embodiments, the rapid
recolonization deployment agent is useful in maintaining or restoring proper gut microbial balance in subjects undergoing antibiotic treatment.

All references cited herein are incorporated by reference in their entirety as though fully set forth. Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Singleton et al., Dictionary of Microbiology and Molecular Biology 3rd ed., J. Wiley & Sons (New York, NY 2001); March, Advanced Organic Chemistry Reactions, Mechanisms and Structure 5th ed., J. Wiley & Sons (New York, NY 2001); and Sambrook and Russell, Molecular Cloning: A Laboratory Manual 3rd ed., Cold Spring Harbor Laboratory Press (Cold Spring Harbor, NY 2001), provide one skilled in the art with a general guide to many of the terms used in the present application.

One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. Indeed, the present invention is in no way limited to the methods and materials described. For purposes of the present invention, the following terms are defined below.

"Mammal" as used herein refers to any member of the class Mammalia, including, without limitation, humans and nonhuman primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, sheep, pigs, goats and horses; domestic mammals such as dogs and cats; laboratory animals including rodents such as mice, rats and guinea pigs, and the like. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be included within the scope of this term.

"Therapeutically effective amount" as used herein refers to that amount which is capable of achieving beneficial results in a patient in need of treatment. A therapeutically effective amount can be determined on an individual basis and will be based, at least in part, on consideration of the physiological characteristics of the mammal, the type of delivery system or therapeutic technique used and the time of administration relative to the progression of the disease.

"Treatment" and "treating," as used herein refer to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent, slow down and/or lessen the disease, or repair the tissue even if the treatment is ultimately unsuccessful.

"Conditions" and "disease conditions," as used herein may include, but are in no way limited to any form disclosed herein.
"Freeze-drying" (also known as lyophilisation, lyophilization or cryodesiccation) as used herein refers to a dehydration process typically used to preserve a perishable material or make the material more convenient for transport and storage. Freeze-drying works by freezing the material and then reducing the surrounding pressure and adding enough heat to allow the frozen water in the material to sublime directly from a solid to a gas.

"Outcome Measures" as used herein refers to the different methods and/or techniques to determine the efficacy of the therapeutic. In particular, as used herein the outcome measures can include the alleviation of symptoms of the given disease, a change in the markers associated with the disease, and/or a change in the histology of the diseased area.

"Time-release" as used herein refers to time release technology and can also be known as sustained-release (SR), sustained-action (SA), extended-release (ER, XR, or XL), time-release or timed-release, controlled-release (CR), modified release (MR), or continuous-release (CR or Contin). Time-release is a mechanism used in pill tablets, capsules, or some other device to dissolve slowly and release a drug over time. Time release technology can comprise a pharmaceutical composition embedded in a matrix of insoluble substances (e.g., some acrylics, chitin, and hydrogels).

"Supportive therapy" as used herein refers to the use of the inventive rapid recolonization deployment agent as a supportive treatment for any other disease, disorder, or condition. The supportive therapy can be implemented in place of another treatment, prior to other treatment, concurrently with other treatment, or post treatment for any disease, disorder, or condition.

As used herein, "subject," may refer to any living creature, preferably an animal, more preferably a mammal, and even more preferably a human.

**Combination therapy:**

Additional aspects provide the herein disclosed inventive methods, further comprising combination therapy, wherein at least one additional therapeutic agent is administered to the patient. In certain aspects, the at least one additional therapeutic agent is selected from the group consisting of steroids, methotrexate, immunosuppressive drugs including cyclophosphamide, cyclosporine, azathioprine and leflunomide, nonsteroidal anti-inflammatory agents such as aspirin, acetaminophen and COX-2 inhibitors, gold agents, antimalarial treatments, steroids (including corticosteroids, eg., hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisolone, methylprednisolone, and prednisone), antacids, sucralfate, H₂ blockers, proton pump inhibitors, prokinetics,
antidiarrheal, antispasmodics, immunomodulators, biologies, anti-inflammatory agents, laxatives, alginic acid, misoprostol, and mosapride.

**Forms of Administration:**

In particular exemplary embodiments, the rapid recolonization deployment agent of the present invention may function as a therapeutic composition alone or in combination with another therapeutic agent such that the therapeutic composition prevents or alleviates at least one symptom of a digestive disorder. The therapeutic compositions of the present invention include compositions that are able to be administered to a subject in need thereof. In certain embodiments, the therapeutic composition formulation may also comprise at least one additional agent selected from the group consisting of: carriers, adjuvants, emulsifying agents, suspending agents, sweeteners, flavorings, perfumes, and binding agents.

As used herein, "pharmacologically acceptable carrier" and "carrier" generally refer to a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some non-limiting examples of materials which can serve as pharmacologically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such as propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

The pharmacologically acceptable carriers described herein, for example, vehicles, adjuvants, excipients, or diluents, are well known to those who are skilled in the art. Typically, the pharmacologically acceptable carrier is chemically inert to the therapeutic agents and has no detrimental side effects or toxicity under the conditions of use. The pharmacologically acceptable carriers can include polymers and polymer matrices, nanoparticles, microbubbles, and the like.
In addition to the therapeutic rapid recolonization deployment agent of the present invention, the therapeutic composition may further comprise inert diluents such as water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Certain embodiments provide for therapeutic compositions comprising the rapid recolonization deployment agent, a pharmaceutical composition or other therapeutic agent or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutical carrier or diluent. These pharmaceutical compositions can be used in the prophylaxis and treatment of the foregoing diseases or conditions and in therapies as mentioned above. Preferably, the carrier must be pharmaceutically acceptable and must be compatible with, i.e. not have a deleterious effect upon, the other ingredients in the composition. The carrier may be a solid or liquid and is preferably formulated as a unit dose formulation, for example, a tablet that may contain from 0.05 to 95% by weight of the active ingredient.

**Administration Routes:**

As one of ordinary skill in the art can readily appreciate, the intestinal tract is complex and composes many different environments beginning with the oral cavity and extending down through the stomach, small intestines and then finally the lower intestines and anus. Each one of these organs has a very different environment that can be challenging to deliver pharmaceutical compositions to and/or through to other sites in the intestinal tract. As such and as can be appreciated by one of ordinary skill in the art, many different methods to deliver pharmaceutical compositions may be useful when practicing this rapid recolonization deployment agent invention. In particular, possible administration routes include oral, sublingual, buccal, rectal, nasal, or insertion of implantable devices or materials (e.g., stents).

Most suitable means of administration for a particular subject will depend on the nature and severity of the disease or condition being treated or the nature of the therapy being used, as well as the nature of the therapeutic composition or additional therapeutic agent. For example, in certain diseases or conditions (e.g., *Clostridium difficile-associated* diarrhea and colitis and ulcerative colitis) the administration routes of treatment can be rectal administration. In certain embodiments, rectal administration is preferred. Further, in other diseases (e.g., Crohn's disease), where it could be necessary for the pharmaceutical
composition to pass through the hostile and very acidic environment of the stomach to reach the appropriate cite of treatment, the administrative route can be oral using an appropriately coated pharmaceutical composition or can be direct treatment (e.g., via direct injection or via tubing) to the cite of the disease or condition. Alternatively, the pharmaceutical composition can be administered to the cite through tubing. This tubing can be introduced through an orifice, including but not limited to nasal, oral, or rectal. Moreover, certain diseases or conditions can have prolonged or intermittent states (e.g., insulin resistance and ulcerative colitis). In these diseases or conditions a method of treatment can have a system for extended treatment (e.g., a stent coated with the rapid recolonization microorganisms, a time-release device or capsule containing these organisms, and implantable pump containing these organisms). According to preferred embodiments, the route of administration for UC and other acute infections is via rectal administration. According to preferred embodiments, prophylactic treatment with the inventive rapid recolonization microorganisms to reduce the effect of antibiotics on gut flora is via oral administration.

In addition to the pharmaceutical compositions described herein, the pharmaceutical compositions can be associated with a type of scaffold (proteinaceous or otherwise), a type of stent coated with the pharmaceutical composition, time/controlled release capsules or devices, and/or an implantable pump. Types of proteinaceous scaffolds are described in Hey, T., et al., "Artificial, non-antibody binding proteins for pharmaceutical and industrial applications," Trends in Biotechnology. 2005;23:514-522.

Formulations suitable for rectal administration include gels, creams, lotions, aqueous or oily suspensions, dispersible powders or granules, emulsions, dissolvable solid materials, douches, and the like. The formulations are preferably provided as unit-dose suppositories comprising the active ingredient in one or more solid carriers forming the suppository base, for example, cocoa butter. Suitable carriers for such formulations include petroleum jelly, lanolin, polyethylene glycols, alcohols, and combinations thereof. Alternatively, colonic washes with the rapid recolonization deployment agent of the present invention may be formulated for colonic or rectal administration.

Formulations suitable for oral administration may be provided as discrete units, such as tablets, capsules, cachets, syrups, elixirs, chewing gum, "lollipop" formulations, microemulsions, solutions, suspensions, lozenges, or gel-coated ampules, each containing a
predetermined amount of the active compound; as powders or granules; as solutions or suspensions in aqueous or non-aqueous liquids; or as oil-in-water or water-in-oil emulsions.

Formulations suitable for transmucosal methods, such as by sublingual or buccal administration include lozenges patches, tablets, and the like comprising the active compound and, typically a flavored base, such as sugar and acacia or tragacanth and pastilles comprising the active compound in an inert base, such as gelatin and glycerine or sucrose acacia.

Formulations of the invention may be prepared by any suitable method, typically by uniformly and intimately admixing the pre-determined gut flora with liquids or finely divided solid carriers or both, in the required proportions and then, if necessary, shaping the resulting mixture into the desired shape. In addition, the pre-determined gut flora will be treated to prolong shelf-life, preferably the shelf-life of the pre-determined gut flora will be extended via freeze drying.

Furthermore, a tablet may be prepared by compressing an intimate mixture comprising a powder or granules of the active ingredient and one or more optional ingredients, such as a binder, lubricant, inert diluent, or surface active dispersing agent, or by molding an intimate mixture of powdered active ingredient of the present invention.

In addition to the ingredients specifically mentioned above, the formulations of the present invention may include other agents known to those skilled in the art, having regard for the type of formulation in issue. For example, formulations suitable for oral administration may include flavoring agents and formulations suitable for intranasal administration may include perfumes.

The therapeutic compositions of the invention can be administered by any conventional method available for use in conjunction with pharmaceutical drugs, either as individual therapeutic agents or in a combination of therapeutic agents.

The dosage administered will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the age, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; and the effect desired. A daily dosage of active ingredient can be expected to be about 0.001 to 1000 milligrams (mg) per kilogram (kg) of body weight.

Dosage forms (compositions suitable for administration) contain from about 1 mg to about 500 mg of active ingredient per unit. In these pharmaceutical compositions, the active
ingredient will ordinarily be present in an amount of about 0.5-95% weight based on the total weight of the composition.

Ointments, pastes, foams, occlusions, creams and gels also can contain excipients, such as starch, tragacanth, cellulose derivatives, silicones, bentonites, silica acid, and talc, or mixtures thereof. Powders and sprays also can contain excipients such as lactose, talc, silica acid, aluminum hydroxide, and calcium silicates, or mixtures of these substances.

Formulations suitable for rectal administration may be presented as suppositories by mixing with a variety of bases such as emulsifying bases or water-soluble bases. Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulas containing, in addition to the active ingredient, such carriers as are known in the art to be appropriate.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

The dose administered to a subject, especially an animal, particularly a human, in the context of the present invention should be sufficient to affect a therapeutic response in the animal over a reasonable time frame. One skilled in the art will recognize that dosage will depend upon a variety of factors including the condition of the animal, the body weight of the animal, as well as the condition being treated. A suitable dose is that which will result in a concentration of the therapeutic composition in a subject that is known to affect the desired response.

The size of the dose also will 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 the therapeutic composition and the desired physiological effect.

It will be appreciated that the compounds of the combination may be administered: (1) simultaneously by combination of the compounds in a co-formulation or (2) by alternation, i.e. delivering the compounds serially, sequentially, in parallel or simultaneously in separate pharmaceutical formulations. In alternation therapy, the delay in administering the second, and optionally a third active ingredient, should not be such as to lose the benefit of a synergistic therapeutic effect of the combination of the active ingredients. According to certain embodiments by either method of administration (1) or (2), ideally the combination should be administered to achieve the most efficacious results. In certain embodiments by
either method of administration (1) or (2), ideally the combination should be administered to achieve peak plasma concentrations of each of the active ingredients.

It will be appreciated by those skilled in the art that the amount of active ingredients in the combinations of the invention required for use in treatment will vary according to a variety of factors, including the nature of the condition being treated and the age and condition of the patient, and will ultimately be at the discretion of the attending physician or health care practitioner. The factors to be considered include the route of administration and nature of the formulation, the animal's body weight, age and general condition and the nature and severity of the disease to be treated.

EXEMPLARY

The following examples are provided to better illustrate the claimed invention and are not to be interpreted as limiting the scope of the invention. To the extent that specific materials are mentioned, it is merely for purposes of illustration and is not intended to limit the invention. One skilled in the art may develop equivalent means or reactants without the exercise of inventive capacity and without departing from the scope of the invention.

EXAMPLE I

fin vitro testing)

According to particular aspects, in vitro analysis of microorganisms that can be useful in treating Clostridium difficile infections and other gastrointestinal disorders, diseases, or conditions which therefore could be useful to include in the current invention for rapid recolonization of the gut is conducted. This in vitro analysis is performed by introducing different combinations of intestinal flora into cultures of C. difficile under a wide variety of different factors and environments, including but not limited to, temperature, acidity, and salt concentration. The different combinations of intestinal flora that can be used can be any one or more of any microorganism or microorganisms, especially if that microorganism is indigenous to the gut flora. More particular combinations of gut flora that can be useful in this Example, include bacteria from the Firmicutes, Bacteroidetes, Actinobacteria, and Euryarchaeota phyla. Examples of gut flora that can be useful in the current invention and could be tested in this in vitro analysis include, but are not limited to, Faecalibacterium prausnitzii, Eubacterium rectale, Ruminococcus bromii, Alistipes putredinis, Subdoligranulum sp, Bacteroides vulgatus, Bacteroides uniformis rel, Parabacteroides
distasonis, Dorea formicigenerans, Roseburia intestinalis, Coprobacillus sp., Anaerostipes caccae, Clostridium sp. BI-114, Clostridium bolteae, Eubacterium halii, Eubacterium eligens, Ruminococcus oheum, Alistipes shahii, Bacteroides stercoris, and Bacteroides massiliensis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus rhamnosus, Lactobacillus zae, Lactobacillus salivarius, Lactobacillus lactis, Lactobacillus helveticus, Lactobacillus reuteri, Lactobacillus amylovorus, Lactobacillus crispatus, Lactobacillus curvatus, Lactobacillus delbrueckii, Lactobacillus gasseri, Lactobacillus johnsonii, Streptococcus thermophilus, Lactobacillus bulgaricus, Lactobacillus brevis, Lactococcus lactis, Lactococcus cremoris, Leuconostoc spp.; Enterococcus faecium, Prevotella species, Methanobrevibacter species (e.g. M. acididurans, M. arboriphilus, M. curvatus, M. cuticularis, M. filiformis, M. gottschalkii, M. millerae, M. olleyae, M. oralis, M. ruminantium, M. smithii, M. thaueri, M. woesei, M. wolini), Pediococcus pentosaceus, Pediococcus acidilactici, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium bifidum, Bifidobacterium infantis, Bifidobacterium lactis, Blautia hansenii, Clostridium scindens, Enterococcus faecalis TX0104, Clostridium asparagiforme, Bacteroides fragilis 3_1_12, Bacteroides intestinalis, Ruminococcus gnavus, Anaerotruncus colihominis, Bacteroides pectinophilus, Clostridium nexile, Clostridium cocoides, Clostridium sp. L2-50, Parabacteroides johnsonii, Bacteroides finegoldii, Butyribrio crossotus, Bacteroides eggerthii, Clostridium sp. M62 1, Coprococcus eutactus, Holdemania filiformis, Clostridium leptum, Streptococcus thermophilus LMD-9, Bacteroides capillosus, Bacteroides dorei, Eubacterium ventriosum, Bacteroides sp. D4, Bacteroides sp. Dl, Coprococcus comes SL7 1, Bacteroides xylanisolvens XB1A, Bacteroides sp. 2_2_4, Bacteroides sp. 4_3_47FAA, Bacteroides ovatus, Bacteroides sp. 9_1_42FAA, Eubacterium siraeum 70 3, Bacteroides sp. 2_1_7, Collinsella aerofaciens, Ruminococcus lactaris, Ruminococcus sp. SRI 5, Unknown sp. SS3 4, Ruminococcus torques L2-14, Bacteroides thetaotaomicron VPI-5482, Clostridium sp. SS2-1, Bacteroides caccae, Parabacteroides merdae, and propionibacterial species, yeast species and mold species.

According to particular aspects, results from this in vitro analysis allows for the proper determination of the appropriate composition and amounts of each micro-flora used in the inventive rapid recolonization deployment agent and has substantial utility for treating Clostridium difficile infections, irritable bowel syndrome and inflammatory bowel disease, and insulin resistance.
EXAMPLE 2
(The inventive rapid recolonization deployment agent is useful in the treatment of patients with Clostridium difficile-associated diarrhea and colitis)

Clostridium difficile-associated diarrhea and colitis. Clostridia are anaerobic, spore-forming rods (bacilli). C. difficile is the most serious cause of antibiotic-associated diarrhea (AAD) and can lead to pseudomembranous colitis, a severe infection of the colon, often resulting from eradication of the normal gut flora by antibiotics. The C. difficile bacteria, which naturally reside in the body, become overpopulated. This overpopulation is harmful because the bacterium releases toxins that can cause bloating and diarrhea with abdominal pain, which can become severe. Latent symptoms often mimic some flu-like symptoms and can mimic disease flare in patients with inflammatory bowel disease-associated colitis. Clostridium difficile-associated diarrhea and colitis can be treated by discontinuing the antibiotics responsible for the initiation of the infection or by oral administration of metronidazole or vancomycin. However, relapses of C. difficile associated diarrhea have been reported in up to 20% of cases. In addition, there are very few effective treatments for chronic C. difficile infections.

Many studies have shown the efficacious use of fecal bacterotherapy in treating chronic relapsing Clostridium difficile-associated diarrhea and colitis. (Rolfe RD, Helebian S, Finegold SM. Bacterial interference between Clostridium difficile and normal fecal flora. J Infect Dis. 1981;143:470-475; Borriello SP. The influence of the normal flora on Clostridium difficile colonisation of the gut. Ann Med. 1990;22:61-67; Torres JF, Camorlinga M, Munoz O. Inhibitory activity of fecal flora against the multiplication of Clostridium difficile. Arch Invest Med. 1986;17:147-156; Torres JF, Camorlinga M, Munoz O. Neutralization of cytotoxic activity of Clostridium difficile with fecal flora. Arch Invest Med. 1987;18:315-317, all of which are hereby incorporated herein in their entirety and especially for their teachings concerning C. difficile.) In particular, research has shown that bowel flora can be re-established using homogenized human feces and that this feces has been shown to be consistently effective against C. difficile-associated diarrhea without having to resort to the use of vancomycin or metronidazole. (Borody TJ. Flora power—Fecal bacteria cure chronic C. difficile diarrhea. Am J Gastroenterol. 2000;95:3028-3029; Borody, T.J. et al., "Bacterotherapy using fecal flora: toying with human motions," J Clin Gastroenterol, 38: 475-83, 2004, both of which are hereby incorporated herein in their entirety and especially for their teachings concerning C. difficile)
According to particular aspects, the inventive rapid recolonization deployment agent has substantial utility for treating *Clostridium difficile-associated* diarrhea and colitis. Specifically and according to further particular aspects, the inventive rapid recolonization deployment agent containing at least one of *Faecalibacterium prausnitzii*, *Eubacterium rectale*, *Ruminococcus bromii*, *Alistipes putredinis*, *Subdoligranulum* sp., *Bacteroides vulgatus*, *Bacteroides uniformis* rel, *Parabacteroides distasonis*, *Dorea formicigenerans*, *Roseburia intestinalis*, *Coprobacillus sp.*, *Anaerostipes caccae*, *Clostridium spiroforme*, *Dorea longicatena*, *Clostridium* sp. BI-114, *Clostridium* bolteae, *Eubacterium halii*, *Eubacterium eligens*, *Ruminococcus obeum*, *Alistipes shahii*, *Bacteroides stercoris*, and *Bacteroides massiliensis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Lactobacillus zeae*, *Lactobacillus salivarius*, *Lactobacillus lactis*, *Lactobacillus helveticus*, *Lactobacillus reuteri*, *Lactobacillus amyllovorus*, *Lactobacillus crispatus*, *Lactobacillus curvatus*, *Lactobacillus delbrueckii*, *Lactobacillus gasseri*, *Lactobacillus johnsonii*, *Streptococcus thermophilus*, *Lactobacillus bulgaricus*, *Lactobacillus fermentum*, *Lactobacillus brevis*, *Lactococcus lactis*, *Lactococcus cremoris*, *Leuconostoc* spp.; *Enterococcus faecium*, *Prevotella* species, *Methanobrevibacter* species (e.g. *M. acididurans*, *M. arborphilus*, *M. curvatus*, *M. cuticularis*, *M. filiformis*, *M. gottschalkii*, *M. millerae*, *M. olleae*, *M. oralis*, *M. ruminantium*, *M. smithii*, *M. thaueri*, *M. wossei*, *M. wolini*), *Pediococcus pentosaceus*, *Pediococcus acidilactici*, *Bifidobacterium longum*, *Bifidobacterium breve*, *Bifidobacterium bifidum*, *Bifidobacterium infantis*, *Bifidobacterium lactis*, *Blautia hansenii*, *Clostridium scindens*, *Enterococcus faecalis* TX0104, *Clostridium asparagiforme*, *Bacteroides fragilis* 3_1-12, *Bacteroides intestinalis*, *Ruminococcus gnavus*, *Anaerotrunclus colihominis*, *Bacteroides pectinophilus*, *Clostridium nexile*, *Clostridium cocoides*, *Clostridium* sp. L2-50, *Parabacteroides johnsonii*, *Bacteroides finegoldii*, *Butyribrio crosstos*, *Bacteroides eggerthii*, *Clostridium* sp. M62 1, *Coprococcus eutactus*, *Holdemania filiformis*, *Clostridium leptum*, *Streptococcus thermophilus* LMD-9, *Bacteroides capillosus*, *Bacteroides dorei*, *Eubacterium ventriosum*, *Bacteroides* sp. D4, *Bacteroides* sp. Dl, *Coprococcus comes* SL7 1, *Bacteroides xylanisolvens* XBJA, *Bacteroides* sp. 2^a2-4, *Bacteroides* sp. 4_3_47FAA, *Bacteroides ovatus*, *Bacteroides* sp. 9_1_42FAA, *Eubacterium siraeum* 70 3, *Bacteroides* sp. 2_1_7, *Collinsella aerofaciens*, *Ruminococcus lacticis*, *Ruminococcus* sp. SRI 5, *Unknown* sp. SS3 4, *Ruminococcus torques* L2-14, *Bacteroides thetaiaotaomicron* VPI-5482, *Clostridium* sp. SS2-1, *Bacteroides caccae*, *Parabacteroides merdae*, and propionibacterial species, yeast species and mold species. According to
preferred embodiments, the rapid recolonization deployment agent is prepared in a shelf-stable formulation and is anally administered to afford for proper treatment.

As will be appreciated in the art, the appropriate dosage and timing of the inventive rapid recolonization deployment agent can be readily determined by one of ordinary skill in the art and can depend on the severity and extent of the infection. In addition, according to particular aspects, the number and repetition of treatments of the inventive rapid recolonization deployment agent can be readily determined by one of ordinary skill in the art and can depend on the severity and extent of the infection.

EXAMPLE 3
(The inventive rapid recolonization deployment agent is useful in the treatment of patients with inflammatory conditions and diseases of the digestive tract (e.g., irritable bowel syndrome and inflammatory bowel disease (e.g., Crohn’s disease and ulcerative colitis))

Inflammatory bowel disease. Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the colon and small intestine. The major types of IBD are Crohn's disease (CD) and ulcerative colitis (UC) and the rising incidence of CD and high prevalence of UC are burdens to the community and the health system. The causes of IBD remain unknown, although accumulating evidence suggests that an excessive mucosal immune response to the enteric flora, or perhaps a specific infectious agent, in combination with genetic predisposition, may be responsible for the chronic inflammatory process.

Crohn’s disease. CD (aka, granulomatous colitis and regional enteritis) is an inflammatory disease that can affect any part of the gastrointestinal tract from mouth to anus, causing a wide variety of symptoms (e.g., abdominal pain, diarrhea (which may be bloody), vomiting, or weight loss, but may also cause complications outside of the gastrointestinal tract such as skin rashes, arthritis and inflammation of the eye. More specifically, CD is an autoimmune disease, caused by the immune system's attacking the gastrointestinal tract and producing inflammation in the gastrointestinal tract.

Interestingly, recent studies have indicated that the gut constituents differ between healthy individuals and individuals suffering from CD. Qin J. et al., (2010) "A human gut microbial gene catalogue established by metagenomic sequencing." Nature 464, 59-65 which is hereby incorporated by reference in its entirety). In particular, certain studies have shown an increase in C. difficile and E. faecalis and a decrease in F. prausnitzii, C. leptum, and R. albus in CD patients compared to healthy individuals. Sokol, H. et al, "Specificities of the fecal microbiota in inflammatory bowel disease," IBD 12:106-1 11, 2006 (which is hereby incorporated by reference in its entirety).

Ulcerative colitis. UC is a form of colitis, a disease of the intestine, specifically the large intestine or colon that includes characteristic ulcers, or open sores, in the colon. The main symptom of active disease is usually constant diarrhea mixed with blood. UC is an intermittent disease, with periods of exacerbated symptoms, and periods that are relatively symptom-free. Although the symptoms of ulcerative colitis can sometimes diminish without any treatment, the disease usually requires treatment to be relatively symptom-free.
UC occurs in 35-100 people for every 100,000 in the United States, and it is more prevalent in northern countries of the world, as well as in northern areas of individual countries or other regions. Although UC has no known cause, there is a presumed genetic component to susceptibility. UC can be triggered in a susceptible person by environmental factors. Current treatment for UC includes: anti-inflammatory drugs, immunosuppression, and biological therapy targeting specific components of the immune response. Surgery to remove part of or the entire colon, colectomy, is conducted occasionally.

Interestingly, recent studies have indicated that the gut constituents differ between healthy individuals and individuals suffering from UC, wherein higher or lower percentages of certain microorganisms can be found. Qin J. et al., (2010) "A human gut microbial gene catalogue established by metagenomic sequencing." Nature 464, 59-65 (which is hereby incorporated by reference in its entirety).


Irritable bowel syndrome (IBS). Irritable bowel syndrome (IBS) (aka, spastic colon) encompasses a variety of diseases causing discomfort in the gastro-intestinal tract (e.g., chronic abdominal pain, discomfort, bloating, altered bowel habits). Diarrhea or constipation may predominate, or they may alternate (classified as IBS-D, IBS-C or IBS-A, respectively). IBS may begin after an infection (post-infectious, IBS-PI) or a stressful life event. Significantly, there is no cure for IBS, but there are treatments which attempt to relieve symptoms (e.g., dietary adjustments, medication and psychological interventions). People with IBS commonly have gastroesophageal reflux.

which are incorporated by reference in their entirety, especially for their teachings concerning IBS and disruption of normal gut flora. Currently, treatment of IBS is managing the systems and often is unsatisfactory. Fecal transfusion can be used to remodel the composition of fecal flora in patients suffering form IBS with gut flora from healthy individuals seems a logical treatment option considering the tentative link between a disturbance in the normal gut flora and IBS. Some studies have suggested that the administration of probiotics both singly or in combination has shown some benefit in alleviating IBS symptoms, including pain and impair bowel function. (Hamilton-Miller JMT. Probiotics in the management of irritable bowel syndrome: a review of clinical trials. Microb Ecol Health Dis. 2001;13: 212-216, Persky SE, Brandt LJ. Treatment of recurrent Clostridium difficile-associated diarrhea by administration of donated stool directly through a colonoscope. Am J Gastroenterol. 2000;95:3283-3285. Borody TJ, Leis S, McGrath K, et al. Treatment of chronic constipation and colitis using human probiotic infusions. In: Probiotics, Prebiotics and New Foods Conference, Universita Urbaniana, Rome, September 2-4, 2001; Andrews PJ, Barnes P, Borody TJ, et al. Chronic constipation reversed by restoration of bowel flora. A case and a hypothesis. Eur J Gastroenterol Hepatol. 1992;4:245-247; which are hereby incorporated by reference in their entirety, especially for their teachings concerning treatment of IBS with gut flora).

According to particular aspects, the inventive rapid recolonization deployment agent has substantial utility for treating irritable bowel syndrome and inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis). Specifically and according to further particular aspects, the inventive rapid recolonization deployment agent containing at least one of Faecalibacterium prausnitzii, Eubacterium rectale, Ruminococcus bromii, Alistipes putredinis, Subdoligranulum sp, Bacteroides vulgatus, Bacteroides uniformis rel, Parabacteroides distasonis, Dorea formicigenerans, Roseburia intestinalis, Coprobacillus sp., Anaerostipes caccae, Clostridium sp., Clostridium sp. Bi-114, Clostridium boletae, Eubacterium halii, Eubacterium eligens, Ruminococcus obeum, Alistipes shahii, Bacteroides stercoris, and Bacteroides massiliensis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus rhamnosus, Lactobacillus zae, Lactobacillus salivarius, Lactobacillus lactis, Lactobacillus helveticus, Lactobacillus reuteri, Lactobacillus amylovorum, Lactobacillus crispatus, Lactobacillus curvatus, Lactobacillus delbrueckii, Lactobacillus gasseri, Lactobacillus johnsonii, Streptococcus thermophilus, Lactobacillus bulgaricus, Lactobacillus fermentum, Lactobacillus brevis, Lactococcus lactis, Lactococcus cremoris, Leuconostoc spp.; Enterococcus faecium, Prevotella species, Methanobrevibacter species (e.g. M. acididurans,
M. arboriphilus, M. curvatus, M. cuticularis, M. filiformis, M. gottschalkii, M. millerae, M.olleyae, M. oralis, M. ruminantium, M. smithii, M. thauieri, M. woesei, M. wolinii), Pediococcus pentosaceus, Pediococcus acidilactici, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium bifidum, Bifidobacterium infantis, Bifidobacterium lactis, Blautia hansenii, Clostridium scindens, Enterococcus faecalis TX0104, Clostridium asparagiforme, Bacteroides fragilis 3_1_12, Bacteroides intestinalis, Ruminococcus gnavus, Anaerotruncus colihominis, Bacteroides pectinophilus, Clostridium nexile, Clostridium cocoides, Clostridium sp. L2-50, Parabacteroides johnsonii, Bacteroides finegoldii, Butyribio crosso, Bacteroides eggerthii, Clostridium sp. M62 1. Coprococcus eutactus, Holdemania filiformis, Clostridium leptum, Streptococcus thermophilus LMD-9, Bacteroides capillosus, Bacteroides dorei, Eubacterium ventriosum, Bacteroides sp. D4, Bacteroides sp. Dl, Coprococcus comes SL7 1, Bacteroides xylanisolvens XB1A, Bacteroides sp. 2_2_4, Bacteroides sp. 4_3_47FAA, Bacteroides ovatus, Bacteroides sp. 9_1_42FAA, Eubacterium siraeum 70 3, Bacteroides sp. 2_1_7, Collinsella aerofaciens, Ruminococcus lactaris, Ruminococcus sp. SRI 5, Unknown sp. SS3 4, Ruminococcus torques L2-14, Bacteroides thetaiotaomicron VPI-5482, Clostridium sp. SS2-1, Bacteroides caccae, Parabacteroides merdae, and propionibacterial species, yeast species and mold species. According to preferred embodiments, the rapid recolonization deployment agent is prepared in a shelf-stable formulation and is analytically administered to afford for proper treatment.

According to preferred aspects, for the treatment of CD, the rapid recolonization deployment agent can contain at least one of F. praussnitzi, C. leptum, and R. albus. According to further preferred aspects, for the treatment of CD, the rapid recolonization deployment agent contains at least F. praussnitzi.

According to preferred aspects, for the treatment of IBS, the rapid recolonization deployment agent can contain at least one of a Lactobacillus, F. praussnitzi, C. leptum, and R. albus. According to further preferred aspects, for the treatment of IBS, the rapid recolonization deployment agent contains at least F. praussnitzi.

According to preferred aspects, for the treatment of UC, the rapid recolonization deployment agent can contain at least one of a Lactobacillus, F. praussnitzi, C. leptum, and R. albus. According to further preferred aspects, for the treatment of UC, the rapid recolonization deployment agent contains at least C. leptum. As will be appreciated in the art, the appropriate dosage and timing of the inventive rapid recolonization deployment agent can be readily determined by one of ordinary skill in the art and can depend on the severity and extent of the disease. In addition, according to particular aspects, the number and repetition
of treatments of the inventive rapid recolonization deployment agent can be readily
determined by one of ordinary skill in the art and can depend on the severity and extent of the
disease.

According to particular aspects, the effectiveness of the inventive rapid recolonization
deployment agent can be followed using certain outcome measures of the specific disease
(e.g., irritable bowel syndrome and inflammatory bowel disease (e.g., Crohn’s disease and
ulcerative colitis). These outcome measures can include: clinical improvement of the patient,
change in certain markers of each specific disease (e.g., microflora-associated biochemical
characteristics and changes in the mucosal imaging and histology of the intestines). (Bennet
JD, Brinkman M. Treatment of ulcerative colitis by implantation of normal colonic flora. 
and colitis using human probiotic infusions. In: Probiotics, Prebiotics and New Foods
Conference, Universita Urbaniana, Rome, September 2-4, 2001; Borody TJ, Warren EF,
1992;4:245-247., each of which is hereby incorporated by reference in their entirety and
especially for their respective teachings of evaluating treatment of fecal transfusions).

Duration of follow-up can vary from between one day to several years post-treatment.

EXAMPLE 4

(The inventive rapid recolonization deployment agent is useful in the treatment of patients
with insulin resistance and/or diabetes)

Insulin resistance. Insulin resistance or metabolic syndrome is a physiological
condition where the hormone, insulin, becomes less effective at lowering blood sugars. The
resulting increase in blood glucose may raise levels outside the normal range and cause
adverse health effects. Certain cell types such as fat and muscle cells require insulin to
absorb glucose. When these cells fail to respond adequately to circulating insulin, blood
glucose levels rise. In addition, the liver helps regulate glucose levels by reducing its
secretion of glucose in the presence of insulin. In individuals with insulin resistance glucose
from their liver is not reduced due to the presence of insulin, thus allowing higher serum
levels of glucose to exist. Moreover, other functions of insulin can also be affected. For
example, insulin resistance in fat cells reduces the normal effects of insulin on lipids and results in reduced uptake of circulating lipids and increased hydrolysis of stored triglycerides. Increased mobilization of stored lipids in these cells elevates free fatty acids in the serum. Elevated blood fatty-acid concentrations (associated with insulin resistance and diabetes mellitus Type 2), reduces muscle glucose uptake, and increases liver glucose production which contribute further to elevated serum glucose levels. High plasma levels of insulin and glucose due to insulin resistance are a major component of the metabolic syndrome.

Recently, a group from the Academic Medical Center in Amsterdam has shown significant improvement in the insulin sensitivity of obese patients with metabolic syndrome using fecal transplants from donors who were healthy and thin. (Fiore, "Fecal Transplant Flashes Insulin Resistance", Medpage Today, Sept. 22, 2010, www.medpagetoday.com, citing to results discussed in Vrieze A, et al, "Metabolic effects of transplanting gut microbiota from lean donors to subjects with metabolic syndrome" European Association of the Study of Diabetes 2010; Abstract 90, which is hereby incorporated by reference in its entirety and especially for its teachings related to fecal transplants and insulin resistance).

These researchers reported that after approximately six weeks, the peripheral insulin sensitivity of the eighteen patients receiving the fecal transplant from the thin donors had improved significantly when compared to those patients who had a fecal transplant from themselves. In addition, the report stated that animal studies confirmed the link between gut microbial flora and obesity. In particular, bacteria from the feces of either obese or lean mice were given to animals. These treated animals then either had a significant increase in total body fat or were leaner according to the mouse body type that from which the bacteria were collected. Thus, there are significant data to support fecal transplants having utility in treating obesity and/or insulin resistance.

According to particular aspects, the inventive rapid recolonization deployment agent has substantial utility for treating insulin resistance and metabolic syndrome. Specifically and according to further particular aspects, the inventive rapid recolonization deployment agent containing at least one of Faecalibacterium prausnitzii, Eubacterium rectale, Ruminococcus bromii, Alistipes putredinis, Subdoligranulum sp, Bacteroides vulgatus, Bacteroides uniformis rel, Parabacteroides distasonis, Dorea formigenerans, Roseburia intestinalis, Coprobacillus sp., Anaerostipes caccae, Clostridium spiroforme, Dorea longicatena, Clostridium sp. BI-114, Clostridium bolteae, Eubacterium halii, Eubacterium eligens, Ruminococcus obeum, Alistipes shahii, Bacteroides stercoris, and Bacteroides massiliensis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei,
Lactobacillus rhamnosus, Lactobacillus zeae, Lactobacillus salivarius, Lactobacillus lactis, Lactobacillus helveticus, Lactobacillus reuteri, Lactobacillus amylovorus, Lactobacillus crispatus, Lactobacillus curvatus, Lactobacillus delbrueckii, Lactobacillus gasseri, Lactobacillus johnsonii, Streptococcus thermophilus, Lactobacillus bulgaricus, Lactobacillus fermentum, Lactobacillus brevis, Lactococcus lactis, Lactococcus cremoris, Leuconostoc spp.; Enterococcus faecium, Prevotella species, Methanobrevibacter species (e.g. M. acidurans, M. arborophilus, M. curvatus, M. cuticularis, M. filiformis, M. gottschalkii, M. millerae, M. oligae, M. oralis, M. ruminantium, M. smithii, M. thaueri, M. woesei, M. wolinitii), Pediococcus pentosaceus, Pediococcus acidilactici, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium bifidum, Bifidobacterium infantis, Bifidobacterium lactis, Blautia hansenii, Clostridium scindens, Enterococcus faecalis TX0104, Clostridium asparagiforme, Bacteroides fragilis 3_1_12, Bacteroides intestinalis, Ruminococcus gnavus, Anaerotruncus colihominis, Bacteroides pectinophilus, Clostridium nexile, Clostridium cocoides, Clostridium sp. L2-50, Parabacteroides johnsonii, Bacteroides finegoldii, Butyribivibrio crosstus, Bacteroides eggerthii, Clostridium sp. M62 1, Coprococcus eutactus, Holdemania filiformis, Clostridium leptum, Streptococcus thermophilus LMD-9, Bacteroides capillosus, Bacteroides dorei, Eubacterium ventriosum, Bacteroides sp. D4, Bacteroides sp. Dl, Coprococcus comes SL7 1, Bacteriodes xylanisolvens XBIA, Bacteroides sp. 2^2_4, Bacteroides sp. 4_3_47FAA, Bacteroides ovatus, Bacteroides sp. 9_1_42FAA, Eubacterium siraeum 70 3, Bacteroides sp. 2_1_7, Collinsella aerofaciens, Ruminococcus lactaris, Ruminococcus sp. SRI 5, Unknown sp. SS3 4, Ruminococcus torques L2-14, Bacteroides thetaotaomicron VPI-5482, Clostridium sp. SS2-1, Bacteroides caccae, Parabacteroides merdae, and propionibacterial species, yeast species and mold species. According to preferred embodiments, the inventive rapid recolonization deployment agent can be prepared in a shelf-stable formulation and can be orally administered to afford for proper treatment.

According to preferred aspects, for the treatment of metabolic disorder and/or insulin resistance and/or diabetes, the rapid recolonization deployment agent can contain at least one of Faecalibacterium prausnitzii and Eubacterium rectale.

As will be appreciated in the art, the appropriate dosage and timing of the inventive rapid recolonization deployment agent can be readily determined by one of ordinary skill in the art and can depend on the severity and extent of the insulin resistance syndrome. In addition, according to particular aspects, the number and repetition of treatments of the inventive rapid recolonization deployment agent can be readily determined by one of...
ordinary skill in the art and can depend on the severity and extent of the insulin resistance syndrome.

According to particular aspects, the effectiveness of the inventive rapid recolonization deployment agent can be followed using certain outcome measures of the insulin resistance syndrome. These outcome measures can include: clinical improvement of the patient, lower serum glucose levels, and change in the insulin resistance of the patient.

Various embodiments of the invention are described above in the Detailed Description. While these descriptions directly describe the above embodiments, it is understood that those skilled in the art may conceive modifications and/or variations to the specific embodiments shown and described herein. Any such modifications or variations that fall within the purview of this description are intended to be included therein as well. Unless specifically noted, it is the intention of the inventors that the words and phrases in the specification and claims be given the ordinary and accustomed meanings to those of ordinary skill in the applicable art(s).

The foregoing description of various embodiments of the invention known to the applicant at this time of filing the application has been presented and is intended for the purposes of illustration and description. The present description is not intended to be exhaustive nor limit the invention to the precise form disclosed and many modifications and variations are possible in the light of the above teachings. The embodiments described serve to explain the principles of the invention and its practical application and to enable others skilled in the art to utilize the invention in various embodiments and with various modifications as are suited to the particular use contemplated. Therefore, it is intended that the invention not be limited to the particular embodiments disclosed for carrying out the invention.

While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that, based upon the teachings herein, changes and modifications may be made without departing from this invention and its broader aspects and, therefore, the appended claims are to encompass within their scope all such changes and modifications as are within the true spirit and scope of this invention. It will be understood by those within the art that, in general, terms used herein are generally intended as "open" terms (e.g., the term "including" should be interpreted as "including but not limited to," the term "having" should be interpreted as "having at least," the term "includes" should be interpreted as "includes but is not limited to," etc.).
CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising a pre-selected combination of microorganisms useful in the treatment of an intestinal disorder, condition or disease.

2. The pharmaceutical composition of claim 1, wherein the intestinal disorders, conditions, or diseases are selected from a bacterial infection, irritable bowel syndrome (IBS) or spastic colon, idiopathic ulcerative colitis, mucous colitis, collagenous colitis, Crohn's disease, inflammatory bowel disease, antibiotic-associated colitis, gastrointestinal cancer and idiopathic or simple constipation.

3. The pharmaceutical composition of claim 2, wherein the bacterial infection is at least one of *H. pylori*, *Salmonella*, *Shigella*, *Staphylococcus*, *Campylobacter*, *Clostridium*, *Escherichia coli*, *Yersinia*, and *Vibrio*.

4. The pharmaceutical composition of claim 3, wherein the bacterial infection is *Clostridium*.

5. The pharmaceutical composition of claim 2, wherein gastrointestinal cancer is at least one of stomach cancer, esophageal cancer, colon cancer, gallbladder cancer, liver cancer, pancreatic cancer, colorectal cancer, anal cancer, and gastrointestinal stromal tumors.

6. The pharmaceutical composition of claim 1, wherein the pre-selected combination of microorganisms includes at least one of *Faecalibacterium prausnitzii*, *Eubacterium rectale*, *Ruminococcus bromii*, *Alistipes putredinis*, *Subdoligranulum sp*, *Bacteroides vulgatus*, *Bacteroides uniformis rel*, *Parabacteroides distasonis*, *Dorea formicigenerans*, *Roseburia intestinalis*, *Coprobacillus sp.*, *Anaerostipes caccae*, *Clostridium spiroforme*, *Dorea longicatena*, *Clostridium sp. BI-114*, *Clostridium bolteae*, *Eubacterium halii*, *Eubacterium eligens*, *Ruminococcus obeum*, *Alistipes shahii*, *Bacteroides stercoris*, and *Bacteroides massiliensis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Lactobacillus zeae*, *Lactobacillus salivarius*, *Lactobacillus lactis*, *Lactobacillus helveticus*, *Lactobacillus reuteri*, *Lactobacillus amylovorus*, *Lactobacillus crispatus*, *Lactobacillus curvatus*, *Lactobacillus delbrueckii*, *Lactobacillus gasseri*, *Lactobacillus johnsonii*, *Streptococcus thermophilus*, *Lactobacillus bulgaricus*, *Lactobacillus fermentum*, *Lactobacillus brevis*, *Lactococcus lactis*, *Lactococcus*. 
cremoris, Leuconostoc spp.; Enterococcus faecium, Prevotella species, Methanobrevibacter species (e.g. M. acididurans, M. arboriphilus, M. curvatus, M. cuticularis, M. filiformis, M. gottschalkii, M. millerae, M.olleyae, M. oralis, M. ruminantium, M. smithii, M. thaueri, M. woesei, M. wolinii), Pediococcus pentosaceus, Pediococcus acidilactici, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium bifidum, Bifidobacterium infantis, Bifidobacterium lactis, Blautia hansenii, Clostridium scindens, Enterococcus faecalis TX0104, Clostridium asparagiforme, Bacteroides fragilis 3_1_12, Bacteroides intestinalis, Ruminococcus gnarus, Anaerotruncus colihominis, Bacteroides pectinophilus, Clostridium nexile, Clostridium cocoides, Clostridium sp. L2-50, Parabacteroides johnsonii, Bacteroides finegoldii, Butyribibrio crosotus, Bacteroides eggerthii, Clostridium sp. M62 1, Coprococcus eutactus, Holdemania filiformis, Clostridium leptum, Streptococcus thermophilus LMD-9, Bacteroides capillosus, Bacteroides dorei, Eubacterium ventriosum, Bacteroides sp. D4, Bacteroides sp. Dl, Coprococcus comes SL7 1, Bacteroides xylanisolvens XB1A, Bacteroides sp. 2_2_4, Bacteroides sp. 4_3_47FAA, Bacteroides ovatus, Bacteroides sp. 9_1_42FAA, Eubacterium siraeum 70 3, Bacteroides sp. 2_1_7, Collinsella aerofaciens, Ruminococcus lactaris, Ruminococcus sp. SRI 5, Unknown sp. SS3 4, Ruminococcus torques L2-14, Bacteroides thetaiotaomicron VPI-5482, Clostridium sp. SS2-1, Bacteroides caccae, Parabacteroides merdae, and propionibacterial species, yeast species and mold species

7. The pharmaceutical composition of claim 1, wherein the combination of microorganisms is administered utilizing at least one of a capsule, tube, suppository, device, and enema.

8. The pharmaceutical composition of claim 1, wherein the combination of microorganisms further comprises a shelf-stable formulation.

9. A pharmaceutical composition comprising a pre-selected combination of microorganism useful in the treatment of diabetes, insulin resistance syndrome and/or metabolic syndrome or a symptom thereof.

10. The pharmaceutical composition of claim 9, wherein the pre-selected combination of microorganisms includes at least one of Faecalibacterium prausnitizii, Eubacterium rectale, Ruminococcus bromii, Alistipes putredinis, Subdoligranulum sp, Bacteroides
vulgatus, Bacteroides uniformis rel, Parabacteroides distasonis, Dorea formicigenerans, Roseburia intestinalis, Coprobacillus sp., Anaerostipes caccae, Clostridium spiroforme, Dorea longicatena, Clostridium sp. BI-114, Clostridium bolteae, Eubacterium halii, Eubacterium eligens, Ruminococcus obeum, Alistipes shahii, Bacteroides stercoris, and Bacteroides massiliensis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus rhamnosus, Lactobacillus zeae, Lactobacillus salivarius, Lactobacillus lactis, Lactobacillus helveticus, Lactobacillus reuteri, Lactobacillus amylovorus, Lactobacillus crispatus, Lactobacillus curvatus, Lactobacillus delbrueckii, Lactobacillus gasseri, Lactobacillus johnsonii, Streptococcus thermophilus, Lactobacillus bulgaricus, Lactobacillus fermentum, Lactobacillus brevis, Lactococcus lactis, Lactococcus cremoris, Leuconostoc spp.; Enterococcus faecium, Prevotella species, Methanobrevibacter species (e.g. M. acididurans, M. arboriphilus, M. curvatus, M. cuticularis, M. filiformis, M. gottschalkii, M. millerae, M.olleyae, M. oralis, M. ruminantium, M. smithii, M. thaueri, M. woesei, M. wolfinii), Pediococcus pentosaceus, Pediococcus acidilactici, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium bifidum, Bifidobacterium infantis, Bifidobacterium lactis, Blautia hansenii, Clostridium scindens, Enterococcus faecalis TX0104, Clostridium asparagiiforme, Bacteroides fragilis 3_1_12, Bacteroides intestinalis, Ruminococcus gnarus, Anaerotruncus colihominis, Bacteroides pectinophilus, Clostridium nexile, Clostridium coccoide, Clostridium sp. L2-50, Parabacteroides johnsonii, Bacteroides finegoldii, Butyrvibrio crosotus, Bacteroides eggerthii, Clostridium sp. M62 1, Coprococcus eutactus, Holdemania filiformis, Clostridium leptum, Streptococcus thermophilus LMD-9, Bacteroides capillosus, Bacteroides dorei, Eubacterium ventriosum, Bacteroides sp. D4, Bacteroides sp. DI, Coprococcus comes SL7 1, Bacteroides xylanisolvens XB1A, Bacteroides sp. 2_2_4, Bacteroides sp. 4_3_47FAA, Bacteroides ovatus, Bacteroides sp. 9_1_42FAA, Eubacterium siraenum 70 3, Bacteroides sp. 2_1_7, Collinsella aerofaciens, Ruminococcus lactaris, Ruminococcus sp. SRI 5, Unknown sp. SS3 4, Ruminococcus torques L2-14, Bacteroides thetaiotaomicron VPI-5482, Clostridium sp. SS2-1, Bacteroides caccae, Parabacteroides merdae, and propionibacterial species, yeast species and mold species
11. The pharmaceutical composition of claim 9, wherein the combination of microorganisms is administered using at least one of a capsule, tube, suppository, device, and enema.

12. The pharmaceutical composition of claim 9, wherein the combination of microorganisms further comprises a shelf-stable formulation.


14. The pharmaceutical composition of claim 13, wherein the pre-selected combination of microorganisms includes at least one of Faecalibacterium prausnitzii, Eubacterium rectale, Ruminococcus bromii, Alistipes putredinis, Subdoligranulum sp, Bacteroides vulgatus, Bacteroides uniformis rel, Parabacteroides distasonis, Dorea formicigenerans, Roseburia intestinalis, Coprobacillus sp., Anaerostipes caccae, Clostridium spiroforme, Dorea longicatena, Clostridium sp. BI-114, Clostridium bolteae, Eubacterium halii, Eubacterium eligens, Ruminococccus obeum, Alistipes shahii, Bacteroides stercoris, and Bacteroides massiliensis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus rhamnosus, Lactobacillus zeae, Lactobacillus salivarius, Lactobacillus lactis, Lactobacillus helveticus, Lactobacillus reuteri, Lactobacillus amylovorus, Lactobacillus crispatus, Lactobacillus curvatus, Lactobacillus delbrueckii, Lactobacillus gasseri, Lactobacillus johnsonii, Streptococcus thermophilus, Lactobacillus bulgaricus, Lactobacillus fermentum, Lactobacillus brevis, Lactococcus lactis, Lactococcus cremoris, Leuconostoc spp., Enterococcus faecium, Prevotella species, Methanobrevibacter species (e.g. M. acidurans, M. arboriphilus, M. curvatus, M. cuticularis, M. filiformis, M. gottschalkii, M. millerae, M. olleyae, M. oralis, M. ruminantium, M. smithii, M. thaueri, M. woesei, M. wolinnii), Pediococcus pentosaceus, Pediococcus acidilactici, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium bifidum, Bifidobacterium infantis, Bifidobacterium lactis, Blautia hansenii, Clostridium scindens, Enterococcus faecalis TX0104, Clostridium asparagiforme, Bacteroides fragilis 3.1.12, Bacteroides intestinalis, Ruminococcus gnarus, Anaerotruncus colihominis, Bacteroides pectinophilus, Clostridium nexile, Clostridium cocoides, Clostridium sp. L2-50, Parabacteroides johnsonii, Bacteroides finegoldii, Butyrivibrio crosstotus, Bacteroides eggerthii, Clostridium sp. M62 1, Coprococcus eutactus, Holdemania filiformis, Clostridium leptum,
Streptococcus thermophilus LMD-9, Bacteroides capillosus, Bacteroides dorei, Eubacterium ventriosum, Bacteroides sp. D4, Bacteroides sp. D1, Coprococcus comes SL7 1, Bacteroides xylanisolvens XB1A, Bacteroides sp. 2_2_4, Bacteroides sp. 4_3_47FAA, Bacteroides ovatus, Bacteroides sp. 9_1_42FAA, Eubacterium siraeum 703, Bacteroides sp. 2_1_7, Collinsella aerofaciens, Ruminococcus lactaris, Ruminococcus sp. SRI 5, Unknown sp. SS3 4, Ruminococcus torques L2-14, Bacteroides thetaiotaomicron VPI-5482, Clostridium sp. SS2-1, Bacteroides caccae, Parabacteroides merdae, and propionibacterial species, yeast species and mold species.

15. The pharmaceutical composition of claim 13, wherein the combination of microorganisms is administered using at least one of a capsule, suppository, device, and enema.

16. The pharmaceutical composition of claim 13, wherein the combination of microorganisms further comprises a shelf-stable formulation.

17. A method of treating an intestinal disease, disorder or symptom thereof, comprising:

- providing a composition capable of reestablishing the intestinal flora; and
- administering a therapeutically effective amount of the composition to a subject in need thereof.

18. The method of claim 17, wherein the composition is capable of having a prolonged shelf-life.

19. The method of claim 17, wherein the composition contains at least one of Faecalibacterium prausnitzii, Eubacterium rectale, Ruminococcus bromii, Alistipes putredinis, Subdoligranulum sp, Bacteroides vulgatus, Bacteroides uniformis rel, Parabacteroides distasonis, Dorea formicigenerans, Roseburia intestinalis, Coprobacillus sp., Anaerostipes caccae, Clostridium spiroforme, Dorea longicatena, Clostridium sp. BI-114, Clostridium boltiae, Eubacterium halii, Eubacterium eligens, Ruminococcus obeum, Alistipes shahii, Bacteroides stercoris, and Bacteroides massiliensis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus rhamnosus, Lactobacillus zeae, Lactobacillus salivarius, Lactobacillus lactis, Lactobacillus helveticus, Lactobacillus reuteri, Lactobacillus amylovorus, Lactobacillus crispatus, Lactobacillus curvatus, Lactobacillus delbrueckii, Lactobacillus gasseri, Lactobacillus johnsonii, Streptococcus thermophilus,
Lactobacillus bulgaricus, Lactobacillus fermentum, Lactobacillus brevis, Lactococcus lactis, Lactococcus cremoris, Leuconostoc spp.; Enterococcus faecium, Prevotella species, Methanobrevibacter species (e.g. M. acididurans, M. arboriphilus, M. curvatus, M. cuticularis, M. filiformis, M. gottschalkii, M. millerae, M. oralis, M. ruminantium, M. smithii, M. thaueri, M. woesei, M. wolini), Pediococcus pentosaceus, Pediococcus acidilactici, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium bifidum, Bifidobacterium infantis, Bifidobacterium lactis, Blautia hansenii, Clostridium scindens, Enterococcus faecalis TX0104, Clostridium asparagiforme, Bacteroides fragilis 3_1_12, Bacteroides intestinalis, Ruminococcus gnarus, Anaerotruncus colihominis, Bacteroides pectinophilus, Clostridium nexilte, Clostridium coccoide, Clostridium sp. L2-50, Parabacteroides johnsonii, Bacteroides finegoldii, Butyryrivibrio crosstus, Bacteroides eggerthii, Clostridium sp. M62 1, Coprococcus eutactus, Holdemania filiformis, Clostridium leptum, Streptococcus thermophilus LMD-9, Bacteroides capillosus, Bacteroides dorei, Eubacterium ventriosum, Bacteroides sp. D4, Bacteroides sp. D1, Coprococcus comes SL7 1, Bacteriodes xylanisolvens XB1A, Bacteroides sp. 2_2_4, Bacteroides sp. 4_3_47FAA, Bacteroides ovatus, Bacteroides sp. 9_1_42FAA, Eubacterium siraeum 70 3, Bacteroides sp. 2_1_7, Collinsella aerofaciens, Ruminococcus lactaris, Ruminococcus sp. SRI 5, Unknown sp. SS3 4, Ruminococcus torques L2-14, Bacteroides thetaiotaomicron VPI-5482, Clostridium sp. SS2-1, Bacteroides caccae, Parabacteroides merdae, and propionibacterial species, yeast species and mold species.

20. The method of claim 17, wherein the intestinal disorder of symptom thereof, is selected from a bacterial infection, irritable bowel syndrome (IBS) or spastic colon, idiopathic ulcerative colitis, mucous colitis, collagenous colitis, Crohn's disease, inflammatory bowel disease, antibiotic-associated colitis, gastrointestinal cancer, and idiopathic or simple constipation.

21. A method of treating insulin resistance or a symptom thereof, comprising:

- providing a composition capable of reestablishing the intestinal flora; and
- administering a therapeutically effective amount of the composition to a subject in need thereof.
22. A method of using a supportive therapy, comprising:

providing a composition capable of rebalancing the intestinal flora; and

administering a therapeutically effective amount of the composition to a subject in need thereof.

23. A kit for the treatment of an intestinal disorder or symptom thereof, comprising:

an agent selected from the group consisting of: *Faecalibacterium prausnitzii*, *Eubacterium rectale*, *Ruminococcus bromii*, *Alistipes putredinis*, *Subdoligranulum* sp, *Bacteroides vulgatus*, *Bacteroides uniformis* rel, *Parabacteroides distasonis*, *Dorea formicigenerans*, *Roseburia intestinalis*, *Coprobacillus* sp., *Anaerostipes c caccae*, *Clostridium spiroforme*, *Dorea longicatena*, *Clostridium sp.* BI-114, *Clostridium bolteae*, *Eubacterium halii*, *Eubacterium eligens*, *Ruminococcus obeum*, *Alistipes shahii*, *Bacteroides stercoris*, and *Bacteroides massiliensis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Lactobacillus zeae*, *Lactobacillus salivarius*, *Lactobacillus lactis*, *Lactobacillus helveticus*, *Lactobacillus reuteri*, *Lactobacillus amylovorus*, *Lactobacillus crispatus*, *Lactobacillus curvatus*, *Lactobacillus delbrueckii*, *Lactobacillus gasseri*, *Lactobacillus johnsonii*, *Streptococcus thermophilus*, *Lactobacillus bulgaricus*, *Lactobacillus fermentum*, *Lactobacillus brevis*, *Lactococcus lactis*, *Lactococcus cremoris*, *Leuconostoc* spp.; *Enterococcus faecium*, *Prevotella* species, *Methanobrevibacter* species (e.g. *M. acididurans*, *M. arborphilus*, *M. curvatus*, *M. curricularis*, *M. filiformis*, *M. gottschalkii*, *M. millerae*, *M. olleyae*, *M. oralis*, *M. ruminantium*, *M. smithii*, *M. thaueri*, *M. woesei*, *M. wollinii*), *Pediococcus pentosaceus*, *Pediococcus acidilactici*, *Bifidobacterium longum*, *Bifidobacterium breve*, *Bifidobacterium bifidum*, *Bifidobacterium infantis*, *Bifidobacterium lactis*, *Blautia hansenii*, *Clostridium scindens*, *Enterococcus faecalis* TX0104, *Clostridium asparagiforme*, *Bacteroides fragilis* 3_1_12, *Bacteroides intestinalis*, *Ruminococcus gnavus*, *Anaerotruncus colihominis*, *Bacteroides pectinophilus*, *Clostridium nexile*, *Clostridium cocoides*, *Clostridium sp.* L2-50, *Parabacteroides johnsonii*, *Bacteroides finegoldii*, *Butyrvibrio crosotus*, *Bacteroides eggerthii*, *Clostridium sp.* M62 1, *Coprococcus eutactus*, *Holdemania filiformis*, *Clostridium leptum*, *Streptococcus thermophilus* LMD-9, *Bacteroides capillosus*, *Bacteroides dorei*, *Eubacterium ventriosum*, *Bacteroides sp.* D4, *Bacteroides sp.* D1, *Coprococcus comes* SL7 1, *Bacteroides xylanisolvens* XB1A, *Bacteroides sp.* 2_2_4, *Bacteroides
sp. 4_3_47FAA, Bacteroides ovatus, Bacteroides sp. 9_1_42FAA, Eubacterium stiraum 70 3, Bacteroides sp. 2_1_7, Collinsella aerofaciens, Ruminococcus lactaris, Ruminococcus sp. SRI 5, Unknown sp. SS3 4, Ruminococcus torques L2-14, Bacteroides thetaiotaomicron VPI-5482, Clostridium sp. SS2-1, Bacteroides caccae, Parabacteroides merdae, and propionibacterial species, yeast species and mold species;

a composition capable of prolonged shelf-life; and

instructions to use the agent to treat the intestinal disorder or symptom thereof.

24. A kit for the treatment of an insulin resistance syndrome or symptom thereof, comprising:

an agent selected from the group consisting of: Faecalibacterium prausnitzii, Eubacterium rectale, Ruminococcus bromii, Alistipes putredinis, Subdoligranulum sp, Bacteroides vulgatus, Bacteroides uniformis rel, Parabacteroides distasonis, Dorea formicigenerans, Roseburia intestinalis, Coprobacillus sp., Anaerostipes caccae, Clostridium spiroforme, Dorea longicatena, Clostridium sp. BI-114, Clostridium bolteae, Eubacterium halii, Eubacterium eligens, Ruminococcus obeum, Alistipes shahii, Bacteroides stercoris, and Bacteroides massiliensis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus rhamnosus, Lactobacillus zeae, Lactobacillus salivarius, Lactobacillus lactis, Lactobacillus helveticus, Lactobacillus reuteri, Lactobacillus amylovorus, Lactobacillus crispatus, Lactobacillus curvatus, Lactobacillus delbrueckii, Lactobacillus gasseri, Lactobacillus johnsonii, Streptococcus thermophilus, Lactobacillus bulgaricus, Lactobacillus fermentum, Lactobacillus brevis, Lactococcus lactis, Lactococcus cremoris, Leuconostoc spp.; Enterococcus faecium, Prevotella species, Methanobrevibacter species (e.g. M. acidurans, M. arboriphilus, M. curvatus, M. curricularis, M. filiformis, M. gottschalkii, M. millerae, M.olleyae, M. oralis, M. ruminantium, M. smithii, M. thaueri, M. woesei, M. wolinni), Pediococcus pentosaceus, Pediococcus acidilactici, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium bifidum, Bifidobacterium infantis, Bifidobacterium lactis, Blautia hansenii, Clostridium scindens, Enterococcus faecalis TX0104, Clostridium asparagiforme, Bacteroides fragilis 3_1_12, Bacteroides intestinalis, Ruminococcus gnavus, Anaerotruncus colihominis, Bacteroides pectinophilus, Clostridium nexile, Clostridium coccoides, Clostridium sp. L2-50, Parabacteroides johnsonii,
Bacteroides finegoldii, Butyrivibrio crossotus, Bacteroides eggerthii, Clostridium sp. M62 1, Coprococcus eutactus, Holdemania filiformis, Clostridium leptum, Streptococcus thermophilus LMD-9, Bacteroides capillosus, Bacteroides dorei, Eubacterium ventriosum, Bacteroides sp. D4, Bacteroides sp. Dl, Coprococcus comes SL7 1, Bacteroides xylanisolvens XB1A, Bacteroides sp. 2_2_4, Bacteroides sp. 4_3_47FAA, Bacteroides ovatus, Bacteroides sp. 9_1_42FAA, Eubacterium siraeum 70 3, Bacteroides sp. 2_1_7, Collinsella aerofaciens, Ruminococcus lactaris, Ruminococcus sp. SRI 5, Unknown sp. SS3 4, Ruminococcus torques L2-14, Bacteroides thetaiotaomicron VPI-5482, Clostridium sp. SS2-1, Bacteroides caccae, Parabacteroides merdae, and propionibacterial species, yeast species and mold species;

a composition capable of prolonged shelf-life; and

instructions to use the agent to treat the insulin resistance syndrome or symptom thereof.
Figure 1

Bacteroides uniformis
Alistipes putredinis
Parabacteroides merdae
Dorea longicatena
Ruminococcus bromii L2-63
Bacteroides caccae
clostridium sp. SS2-1
Bacteroides thetaiotaomicron VPI-5482
Eubacterium hallii
Ruminococcus torques L2-14
Unknown sp. SS3 4
Ruminococcus sp. SR1 5
Faecalibacterium prausnitzii SL3 3
Ruminococcus lactaris
Collinsella aerofaciens
dorea formicigenerans
Bacteroides vulgatus ATCC 8482
Roseburia intestinalis M50 1
Bacteroides sp. 2_1 7
Eubacterium siraeum 70 3
Parabacteroides distasonis ATCC 8503
Bacteroides sp. 9_1 42FAA
Bacteroides ovatus
Bacteroides sp. 4_3 47FAA
Bacteroides sp. 2_2 4
Eubacterium rectale M104 1
Bacteroides xylanisolvens XB1A
coprococcus comes SL7 1
Bacteroides sp. D1
Bacteroides sp. D4
eubacterium ventriosum
Bacteroides dorei
Ruminococcus obeum A2-162
Subdoligranulum variabile
Bacteroides capillosus
Streptococcus thermophilus LMD-9
clostridium leptum
Holdemania filiformis
Bacteroides stercoris
coprococcus eutactus
clostridium sp. M62 1
Bacteroides eggertii
Butyrivibrio crosatus
Bacteroides finegoidii
Parabacteroides johnsonii
clostridium sp. L2-50
clostridium nexile
Bacteroides pectinophilus
anaerotruncus colitihominis
Ruminococcus gravis
Bacteroides intestina
Bacteroides fragilis 3_1 12
clostridium asparagiforme
Enterococcus faecalis TX0104
clostridium scindens
Blautia hansenii
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

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<th>IPC(8)</th>
<th>A61K 39/02 (201)</th>
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<td>424/234.1</td>
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 424/234.1

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
* Search Term: *Samaritan, Cunningham, Probiotic, bactenotherapy, combination, mixture, microorganism, microflora, Clostridium, diabetes, insulin resistance, shell stable,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>X</td>
<td>US 2006/0093592 A1 (Cheruvanyak et al.) 04 May 2006 (04.05.2006), especially para [0006]-[0007], [0012], [0026]-[0027], [0032], [0052], [0067]</td>
<td>1-4, 6-8, 13-20 and 22-23</td>
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<tr>
<td>X</td>
<td>US 6,696,057 B1 (Bojob) 24 February 2004 (24.02.2004), especially col 6, lines 28-50</td>
<td>1-2 and 5-6</td>
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<tr>
<td>X</td>
<td>US 2010/0178281 A1 (Salminen et al.) 15 July 2010 (15.07.2010), especially para [0001], [0005], [0011], [0022], [0025], [0046], [0070]-[0071]</td>
<td>9-12, 21 and 24</td>
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Further documents are listed in the continuation of Box C.

Date of the actual completion of the international search
30 June 2012 (30.06.2012)

Date of mailing of the international search report
17 JUL 2012

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