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(54) **Title**: IMMUNOMODULATORY COMPOSITIONS AND METHODS OF USE THEREOF

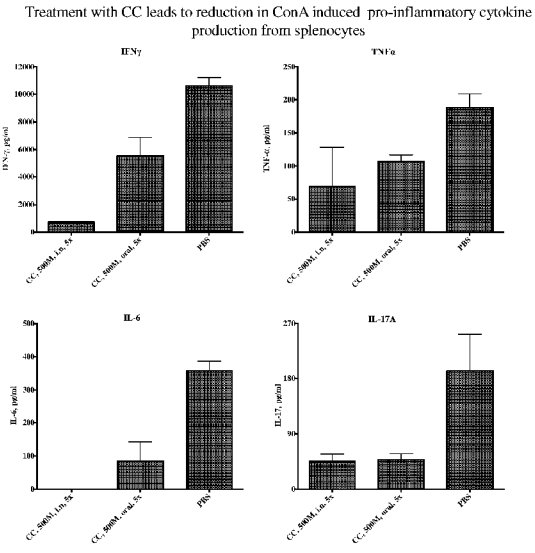

Figure 1

(57) **Abstract**: The present disclosure provides immunomodulatory compositions comprising live Caulobacter crescentus (CC). Immunomodulatory compositions of the present disclosure are useful for modulating an immune response in an individual. The present disclosure thus provides methods of modulating an immune response in an individual, involving administering an immunomodulatory composition comprising live CC to the individual.

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IMMUNOMODULATORY COMPOSITIONS AND METHODS OF USE THEREOF

INTRODUCTION

[0001] *Caulobacter crescentus* is non-pathogenic, harmless, aquatic, gram-negative bacterium that grows at ~23 °C in many soil and freshwater environments Caulobacter has been studied for nearly 50 years. The main laboratory strain (*C. crescentus* CB15) is well characterized genetically and biochemically, and the genome of *C. crescentus* has been sequenced. Caulobacters are readily grown using standard laboratory equipment. They can also be easily grown in commercial fermenters to at least 30 optical density units (ODs) in animal protein free, defined minimal media.

[0002] There is a need in the art for immunomodulatory compositions that can be used in the prophylaxis and/or treatment of disorders such as inflammation, undesirable inflammatory activity, exacerbated immune responses, aberrant immune responses, immune dysregulation and autoimmune diseases.

SUMMARY

[0003] The present disclosure provides immunomodulatory compositions comprising *Caulobacter crescentus* (CC). Immunomodulatory compositions of the present disclosure are useful for modulating an immune response in an individual. The present disclosure provides methods of modulating an immune response in an individual, involving administering an immunomodulatory composition comprising CC to the individual.

BRIEF DESCRIPTION OF THE DRAWINGS

[0004] **FIG.1** demonstrates the reduction in concanavalin A (ConA) induced pro-inflammatory cytokines (IFN-γ, TNF-α, IL-6 and IL-17A) production in splenocytes isolated from CC and PBS treated mice by intranasal and oral routes twice weekly. Data are expressed in pg/ml and shown as average ± standard deviation (SD) of triplicates.

[0005] **FIG.2** demonstrates the reduction in pokeweed mitogen (PWM) induced pro-inflammatory cytokines (IFN-γ, TNF-α, IL-6 and IL-17A) production in splenocytes isolated from CC and phosphate buffered saline (PBS) treated mice by intranasal and oral routes twice weekly. Data are expressed in pg/ml and shown as average ±SD of triplicates.

[0006] **FIG.3A-3C** illustrate the induction of IL-10 in splenocytes isolated from CC and PBS treated mice by intranasal and oral routes twice weekly and stimulated ex vivo for 24 h with medium (A), PWM (B) and ConA (C). Data are expressed in pg/ml and shown as average +SD of triplicates.

[0007] **FIG.4** illustrates the induction profile of IL-10 in splenocytes isolated from CC and PBS treated mice orally twice a week. Cells were stimulated in vitro with LPS for 24 or 72 hrs.

[0008] **FIG.5** shows the reduction profile of cytokines (IFN-γ, IL-6 and IL-17A) in mesenteric lymph nodes isolated from CC and PBS administered mice orally twice a week. Cells were stimulated in vitro with lipopolysaccharide (LPS) for 24 hrs. Data are shown as average +SD.

[0009] **FIG.6** illustrates the enhancement of IL-10 producing CD4+ and CD8+ T cells in splenocytes isolated from CC and PBS fed mice twice weekly. Percent of cells positive for CD3 and CD4 or CD8, expressing intracellular IL-10 are presented.

[0010] **FIG.7** demonstrates the modulation in ConA induced pro-inflammatory cytokines (IFN-γ, TNF-αand IL-6) production in splenocytes isolated from CC and PBS treated mice by subcutaneous route once weekly. Data are expressed in pg/ml and shown as average +SD of triplicates.

[0011] **FIG.8** demonstrates the induction of regulatory lymphocytes (CD8 T cells, NKT cells and NK cells) in mice treated with CC or PBS orally once weekly. The data represent $CD3^+CD8^+$, CD3+CD49b+ and CD3-$CD49b^+$ populations expressing CD25, FoxP3 or PD-1.

[0012] **FIG.9** demonstrates the induction of regulatory lymphocytes (CD4 and CD8 T cells) in mice treated with CC or PBS subcutaneously once weekly. The data represent $CD3^+CD4^+$ and $CD3^+CD8^+$ populations expressing CD25 and FoxP3.

[0013] **FIG.10** shows the modulation of IL-1β, IL-6 and IL-10 in sera samples from CC and PBS treated mice orally post 2 hours (hrs) in vivo challenge with LPS at 7 mg/Kg. The LPS challenged mice has dramatic increase in inflammatory cytokines in sera, which were reduced in mice treated with CC. In contrast CC treatment led to an increase in IL-10 levels in LPS challenged mice.

[0014] **FIG.11** demonstrates the modulation of TNF-α, IL-6, IL-1β, and IL-17A in liver and lung homogenate samples from CC and PBS treated mice orally post 2 hrs in vivo challenge with LPS at 7 mg/kg. CC used was prepared in two formats: CC-1 (CC grown in liquid peptone yeast extract (PYE) medium and stored at room temperature in saline), and CC-2

(CC grown in liquid PYE medium and stored at 4°C in refrigerator). Data represent average + SD of triplicate wells.

[0015] **FIG. 12** illustrates the biochemical parameters (GLU: glucose; GLOB: Globulin; ALT: Alanine aminotransferases; TP: total phosphates; TBIL: total bilirubin) in the sera samples from CC and PBS treated mice orally post 2 hrs in vivo challenge with LPS at 7 mg/Kg. CC used was prepared in two formats: CC-1 (CC grown in liquid PYE medium and stored at room temperature in saline), and CC-2 (CC grown in liquid PYE medium and stored at 4°C in refrigerator).

[0016] **FIG.13** shows hematoxylin and eosin (H& E) staining of the liver sections isolated from CC and PBS treated mice orally post 2 hrs in vivo challenge with LPS at 7 mg/Kg. CC used was prepared in two formats: CC-1 (CC grown in liquid PYE medium and stored at room temperature in saline), and CC-2 (CC grown in liquid PYE medium and stored at 4°C in refrigerator).

[0017] **FIG.14** demonstrates the modulation of cytokines (IFN-γ, IL-6, IL-17A and IL-22) in Aldra (Imiquimod) induced psoriasis mouse model upon two week (5 days/wk) oral treatment with CC and PBS. Splenocytes were harvested from mice and cultured ex vivo for 4 days in medium, followed by collecting supernatant and testing cytokines.

[0018] **FIG.15** demonstrates the modulation of cytokines (IFN-γ, TNF-α, IL-1β, IL-8, MIP-1α) in DSS (Dextran sulfate sodium) induced IBD (inflammatory bowel disease) mouse model. Data are expressed in pg/ml and shown as average±SD of triplicates.

[0019] **FIG.16** demonstrates the suppression of autoantigen specific T cell proliferation and antibody (IgG and IgG2a) responses in an experimental autoimmune encephalomyelitis (EAE) mouse model upon oral treatment with CC.

[0020] **FIG.17** demonstrates the suppression of allergen specific IgE antibody responses in an ovalbumin-induced allergic airway inflammation model upon oral treatment with CC.

[0021] **FIG.18** demonstrates reduction of allergen specific cytokines (IL-4 and IL-6) in spleen in an ovalbumin-induced allergic airway inflammation model upon oral treatment with CC. Data are expressed in pg/ml and shown as average±SD of triplicates.

[0022] **FIG.19** illustrates reduction of allergen specific cytokines (IL-4 and IL-6) in spleen in an ovalbumin-induced allergic airway inflammation model upon oral treatment with CC + dexamethasone (DEX), DEX alone or no treatment control. Data are expressed in pg/ml and shown as average±SD of triplicates.

[0023] **FIG. 20** demonstrates the effect of oral treatment with CC on pro-inflammatory cytokines (IFN-γ, TNF-α, IL-6 and IL-1β) in liver of mice on high fat diet, compared to

untreated high-fat diet fed mice. Data were obtained at ~180 days after initiation of high-fat diet and are shown as mean±SD of 5 mice. Data are expressed in pg/ml and shown as average±SD of triplicates.

[0024] **FIG. 21** shows the effect of oral treatment with CC on pro-inflammatory cytokines (IFN-γ, TNF-α and IL-6) in spleen of mice on high fat diet, compared to untreated high-fat diet fed mice. Data were obtained at ~180 days after initiation of high-fat diet and are shown as mean±SD of 5 mice. Data are expressed in pg/ml.

[0025] **FIG.22** illustrates the biochemical parameters (CHOL: cholesterol, TRIG: triglycerides, URIC: uric acid, CK: creatine kinase) in the sera samples from CC treated mice on high fat diet, and compared to untreated high fat diet fed mice. Data were obtained at ~180 days after initiation of high-fat diet and are shown as mean of 5 mice.

[0026] **FIG. 23** illustrates the effect of CC on glucose tolerance in mice on high fat diet, compared to untreated high-fat diet fed mice. Data were obtained at ~180 days after initiation of high-fat diet and are shown as mean±SD of 5 mice.

[0027] **FIG. 24** illustrates the biochemical parameters (PHOS: phosphate; TBIL: total bilirubin) in the sera samples from CC + cyclophosphamide and cyclophosphamide treated mice bearing EL-4 subcutaneous tumor, and compared to normal mice.

[0028] **FIG. 25** illustrates the biochemical parameters (PHOS: phosphate; UREA; TBIL: total bilirubin; AST: aspartate aminotransferase) in the sera samples from CC + cisplatin and cisplatin treated mice with B16 metastatic cancer, and compared to normal mice.

[0029] **FIG. 26** illustrates the biochemical parameters (ALT: alanine aminotransferases; AST: aspartate aminotransferase) in the sera samples from CC + anti-PD-1 monoclonal antibody and anti-PD-1 monoclonal antibody treated mice with B16 tumor, and compared to normal mice.

[0030] **FIG.27** demonstrates the modulation of IFN-γ, TNF-α, IL-6, IL-1β, MIP-1α, IL-8 and IL-10 in liver homogenate samples from LPS^{-ve} CC and PBS treated mice orally post 2 and 24 hrs in vivo challenge with LPS at 25 mg/Kg, i.p. Data are expressed in pg/ml and represent average ± SD of triplicate wells.

[0031] **FIG. 28** demonstrates that *Caulobacter vibroides* (CV) can lead to down regulation of inflammatory cytokines (IFN-γ and TNF-α) induced by a probiotic (*Lactobacillus rhamnosus, LB*) or a pathogenic bacterium (*Lysteria monocytogenes, LM*) from human PBMCs in cell cultures. Data are expressed in pg/ml and represent average + SD of triplicate wells.

[0032] **FIG. 29** shows that CC induces IL-10 production from human myeloid dendritic cells (DCs) cultured ex vivo. Data are expressed in pg/ml and represent average ± SD of triplicate wells.

[0033] **FIG.30** demonstrates that CC can be used to differentiate/expand myeloid cells from pluripotent stem cells present in human peripheral blood. The data represent $CD34^+CD45^-$, $CD34^+$ $CD45^-CD11c^+$ and $CD34^+CD45^-CD11b^+$ populations as determined by flow cytometry.

DEFINITIONS

[0034] The terms "individual," "host," "subject," and "patient" are used interchangeably herein, and refer to mammals, including, but not limited to, humans, non-human primates (e.g. simians), non-human mammals (e.g., mammalian livestock animals (e.g., bovine, porcine, caprine, and ovine animals)), and mammalian pets (e.g., cats, dogs); fish; and birds (e.g., chicken).

[0035] A "biological sample" encompasses a variety of sample types obtained from an individual. The definition encompasses blood, serum, plasma, and other liquid samples of biological origin; solid tissue samples such as a biopsy specimen or tissue cultures or cells derived therefrom and the progeny thereof. The definition also includes samples that have been manipulated in any way after their procurement, such as by treatment with reagents; washed; or enrichment for certain cell populations, such as epithelial cells. The term "biological sample" encompasses a clinical sample, and also includes cells in culture, cell supernatants, organs, tissue samples, lung biopsy samples, lung epithelial cells, gastrointestinal epithelial cells, gastrointestinal tract tissue samples, bronchoalveolar lavage (BAL) fluid samples, nasal lavage fluid samples, blood, plasma, serum, cerebrospinal fluid, fecal samples, and the like.

[0036] An "immunomodulator" or "immunomodulatory agent" is any agent which does one or more of: restores depressed immune function, down-regulates an abnormal immune function, regulates abnormal/excessive immune function, enhances normal immune function, and provide desired immune response. Immune function includes one or more of: humoral (antibody-mediated) immunity, cellular immunity, and innate immunity. An "immunomodulator" includes agents acting directly on the cells involved in the expression of immune response, or on cellular or molecular mechanisms, which, in turn, act to modify the function of cells involved in immune response. Regulation of immune function may result from the action of an immunomodulatory agent to abrogate activating

mechanisms derived by positive-feedback influences endogenous or exogenous to the immune system. Regulation of immune function may result from the action of an immunomodulatory agent to abrogate suppressing mechanisms derived by negative-feedback influences endogenous or exogenous to the immune system. Thus, immunomodulators can have diverse mechanisms of action.

[0037] The terms “modulate” and “modulation” refer to increasing, reducing, or balancing the number and/or activity of immune cells, cytokines, chemokines, antibodies, soluble factors, surface molecules, intracellular molecules, effector functions, regulatory functions etc.

[0038] The terms “autoimmune disease” and “autoimmune disorder” are used interchangeably herein to refer to diseases characterized by an immune response to a self antigen, i.e., an immune response to substances and tissues normally present in the body.

[0039] The term "inflammatory disease" refers to a disease caused by, resulting from, or resulting in inflammation. The term "inflammatory disease" may also refer to a dysregulated inflammatory reaction that causes an exaggerated response by various innate and adaptive immune cells leading to abnormal tissue damage and/or cell death.

[0040] An “adjuvant” is any agent which is capable of potentiating an immune response and are, therefore, one class of immunopotentiators (Stites and Terr, Basic and Clinical Immunology, 7th Ed., Appleton and Lange Norwalk CT. pp. 797, 1991). Adjuvants are used to increase the immune responses in vaccination in order to enhance the humoral and/or cell mediated immune responses.

[0041] A “cytokine” means any secreted polypeptide that affects the functions of other cells, and is a molecule, which modulates interactions between cells in the immune or inflammatory response. A cytokine includes, but is not limited to monokines, chemokines, and lymphokines, regardless of which cells produce them.

[0042] The terms "antibodies" and “immunoglobulin” include antibodies or immunoglobulins of any isotype, fragments of antibodies which retain specific binding to antigen, including, but not limited to, Fab, Fv, scFv, and Fd fragments, chimeric antibodies, humanized antibodies, single-chain antibodies, bi-specific antibodies, and fusion proteins comprising an antigen-binding portion of an antibody and a non-antibody protein. Also encompassed by the term are Fab', Fv, $F(ab')_2$, and or other antibody fragments that retain specific binding to antigen, and monoclonal antibodies. An antibody may be monovalent or bivalent.

[0043] A "therapeutically effective amount" or "efficacious amount" means the amount of a compound or agent that, when administered to a mammal or other subject for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound or agent, the disease and its severity and the age, weight, general health status, sex, etc., of the subject to be treated. In some cases, an "effective amount" of an agent is an amount that: 1) restores the immune function to normal levels; 2) modulates immune function to normal levels; or 3) reduces immune function to below a pathological level.

[0044] The terms "treatment", "treating" and the like are used herein to generally mean obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a disease and/or adverse effect attributable to the disease. "Treatment" as used herein covers any treatment of a disease or symptom in a mammal, and includes: (a) preventing the disease or symptom from occurring in a subject which may be predisposed to acquiring the disease or symptom but has not yet been diagnosed as having it; (b) inhibiting the disease or symptom, i.e., arresting its development; or (c) relieving the disease, i.e., causing regression of the disease. The therapeutic agent may be administered before, during or after the onset of disease or injury. The treatment of ongoing disease, where the treatment stabilizes or reduces the undesirable clinical symptoms of the patient, is of particular interest. Such treatment is desirably performed prior to complete loss of function in the affected tissues. The subject therapy will desirably be administered during the symptomatic stage of the disease, and in some cases after the symptomatic stage of the disease.

[0045] A "pharmaceutically acceptable carrier or excipient" means a non-toxic solid, semi-solid, or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the particular characteristics of the gent selected, the disease state to be treated, the stage of the disease, and other relevant circumstances.

[0046] Before the present invention is further described, it is to be understood that this invention is not limited to particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0047] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

[0048] Unless defined otherwise, all 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. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

[0049] It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a live *Caulobacter crescentus*" includes a plurality of such bacteria and reference to "the cytokine" includes references to one or more cytokines and equivalents thereof known to those skilled in the art, and so forth. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as "solely," "only" and the like in connection with the recitation of claim elements, or use of a "negative" limitation.

[0050] It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination. All combinations of the embodiments pertaining to the invention are specifically embraced by the present invention and are disclosed herein just as if each and every combination was individually and explicitly disclosed. In addition, all sub-combinations of the various embodiments and elements thereof are also specifically embraced by the present invention and are disclosed herein just as if each and every such sub-combination was individually and explicitly disclosed herein.

[0051] The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

DETAILED DESCRIPTION

[0052] The present disclosure relates to *Caulobacter crescentus* (CC) and its use as an immunomodulatory biotherapeutic agent. CC has been shown to have immunomodulatory effects by modulating innate and adaptive immune responses. The present disclosure provides immunomodulatory compositions comprising live *Caulobacter crescentus* (CC). Immunomodulatory compositions of the present disclosure are useful for modulating an immune response in an individual. Immunomodulatory compositions of the present disclosure are useful for reducing an undesired immune response in an individual. Immunomodulatory compositions of the present disclosure are useful for reducing inflammation in an individual. The present disclosure provides methods of modulating an immune response in an individual, involving administering an immunomodulatory composition comprising CC to the individual. The present disclosure provides methods of reducing an undesired immune response in an individual, involving administering an immunomodulatory composition comprising live CC to the individual. The present disclosure provides methods of reducing inflammation in an individual, involving administering an immunomodulatory composition comprising live CC to the individual.

Immunomodulatory Compositions

[0053] The present disclosure provides immunomodulatory compositions comprising *Caulobacter crescentus* (CC). CC in an immunomodulatory composition of the present disclosure are viable. CC in an immunomodulatory composition can be non-denatured, mutated, attenuated and/or genetically modified. An immunomodulatory composition of the present disclosure can comprise a cocktail of one or more different strains of *Caulobacter crescentus* bacteria.

[0054] CC-containing immunomodulatory compositions include the CC by itself with a pharmaceutically acceptable carrier or excipients for immunomodulatory activity, including "adjuvanting" in which CC administration to a subject may be wholly independent of, and/or separated temporally and/or spatially from, administration to the

subject of one or more antigens against which modulation or regulation of an immune response (e.g., an antigen specific response) in the subject is desired.

[0055] An immunomodulatory composition of the present disclosure can modulate (e.g., reduce) an immune response in an individual. In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number of B cells in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number of B cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, or more than 10-fold, compared to the number of B cells in the individual in the absence of treatment with the immunomodulatory composition. In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number of antigen-specific B cells in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the number of antigen-specific B cells in an individual by 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 75%, or more than 75%, compared to the number of antigen-specific B cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the number of autoantigen-specific B cells in an individual by 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 75%, or more than 75%, compared to the number of autoantigen-specific B cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the number of allergen-specific B cells in an individual by 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 75%, or more than 75%, compared to the number of allergen-specific B cells in the individual in the absence of treatment with the immunomodulatory composition.

[0056] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) activity of B cells in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) activation of B cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the activation level of B cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the activation of B cells in an individual by 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 75%, or more than 75%, compared to the activation level of B cells in the individual in the absence of treatment with the immunomodulatory composition.

[0057] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the amount of antibody specific to a given antigen in the individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the amount of antibody specific to a given antigen in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, or more than 10-fold, compared to the amount of antibody specific to the antigen in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the amount of antibody specific to a given antigen in

an individual by 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 75%, or more than 75%, compared to the amount of antibody specific to the antigen in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the amount of autoantigen-specific antibody in an individual by 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 75%, or more than 75%, compared to the amount of autoantigen-specific antibody in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the amount of allergen-specific antibody in an individual by 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 75%, or more than 75%, compared to the amount of allergen-specific antibody in the individual in the absence of treatment with the immunomodulatory composition.

[0058] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) production of one or more cytokines in the individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) production of one or more cytokines in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, or more than 10-fold, compared to the amount of the cytokine in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the production of one or more cytokines in an individual by 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 75%, or more than 75%, compared to the production of one or more cytokines in the individual in the absence of treatment with the immunomodulatory

composition. In other cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) production of GM-CSF in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, or more than 10-fold, compared to the amount of GM-CSF in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the production of GM-CSF in an individual by 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 75%, or more than 75%, compared to the amount of GM-CSF in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) production of IL-22 in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, or more than 10-fold, compared to the amount of IL-22 in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the production of IL-22 in an individual by 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 75%, or more than 75%, compared to the amount of IL-22 in the individual in the absence of treatment with the immunomodulatory composition. In other, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) production of interferon (IFN)-α and/or IFN-β and/or IFN-γ in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, or more than 10-fold, compared to the amount of IFN-α or IFN-β or IFN-γ in the individual in the absence of treatment with the immunomodulatory

composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the production of interferon (IFN)-α and/or IFN-β and/or IFN-γ in an individual by 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 75%, or more than 75%, compared to the amount of interferon (IFN)-α and/or IFN-β and/or IFN-γ in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the production of IFN-γ in an individual by 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 75%, or more than 75%, compared to the amount of IFN-γ in the individual in the absence of treatment with the immunomodulatory composition.

[0059] As another example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) production of one or more of IL-1β, IL-17A, IL-2, IL-10, IL-6 and TNF-α in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, or more than 10-fold, compared to the amount of IL-1β, IL-17A, IL-2, IL-10, IL-6, or TNF-α in the individual in the absence of treatment with the immunomodulatory composition. In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to increase the level of IL-10 in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, or more than 10-fold, compared to the amount of IL-10 in the individual in the absence of treatment with the immunomodulatory composition. In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to increase the number of IL-10-producing $CD4^+$ and/or $CD8^+$ T cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, or more than 10-fold, compared to the number of IL-10-

producing $CD4^+$ and/or $CD8^+$ T cells in the individual in the absence of treatment with the immunomodulatory composition. As another example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the production of one or more of IL-1β, IL-17A, IL-2, IL-6 and TNF-α in an individual by 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 75%, or more than 75%, compared to the amount of one or more of IL-1 β, IL-17A, IL-2, IL-6 and TNF-α in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the production of IL-17 in an individual by 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 75%, or more than 75%, compared to the amount of IL-17 in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the production of IL-2 in an individual by 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 75%, or more than 75%, compared to the amount of IL-2 the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the production of TNF-α in an individual by 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 75%, or more than 75%, compared to the amount of TNF-α in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the production of IL-6 in an individual by 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 75%, or more than 75%, compared to the amount of IL-6 in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of

the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the production of IL-1β in an individual by 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 75%, or more than 75%, compared to the amount of IL-1β in the individual in the absence of treatment with the immunomodulatory composition. In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to increase the level of TGF-β in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, or more than 10-fold, compared to the amount of TGF-β in the individual in the absence of treatment with the immunomodulatory composition.

[0060] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., increase, reduce or balance) production of one or more cytokines, chemokines or lymphotoxins such as but not limited to GM-CSF, IL-2, IL-22, Interferons, IL-1β, TGF-β, IL-17A, IL-2, IL-10, IL-6, IL-5, IL-13, TNF-α, IL-9, IL-28, KC/IL-8, MIP-1α, LTα4 etc. in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, or more than 10-fold, compared to the amount of cytokines, chemokines or lymphotoxins such as but not limited to GM-CSF, IL-2, IL-22, Interferons, IL-1β, TGF-β, IL-17A, IL-2, IL-10, IL-6, IL-5, IL-13, TNF-α, IL-9, IL-28, KC/IL-8, MIP-1α, LTα4 etc. in the individual in the absence of treatment with the immunomodulatory composition.

[0061] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) a Th1 response in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) a Th1 response in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-

fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the level of the Th1 response in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce a Th1 response in an individual by 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 75%, or more than 75%, compared to the Th1 response in the individual in the absence of treatment with the immunomodulatory composition.

[0062] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of $CD4^+$ T cells in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of $CD4^+$ T cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number and/or activity of $CD4^+$ T cells in the individual in the absence of treatment with the immunomodulatory composition. In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of antigen-specific $CD4^+$ T cells in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of antigen-specific $CD4^+$ T cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number and/or activity of antigen-specific $CD4^+$ T cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an

immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the number and/or activity of $CD4^+$ T cells in an individual by 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 75%, or more than 75%, compared to the number and/or activity of $CD4^+$ T cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the number and/or activity of antigen-specific $CD4^+$ T cells in an individual by 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 75%, or more than 75%, compared to the number and/or activity of antigen-specific $CD4^+$ T cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the number and/or activity of autoantigen-specific $CD4^+$ T cells in an individual by 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 75%, or more than 75%, compared to the number and/or activity of autoantigen-specific $CD4^+$ T cells in the individual in the absence of treatment with the immunomodulatory composition.

[0063] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of $CD8^+$ T cells in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of $CD8^+$ T cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number and/or activity of $CD8^+$ T cells in the individual in the absence of treatment with the immunomodulatory composition. In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to

modulate (e.g., reduce) the number and/or activity of antigen-specific $CD8^+$ T cells in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of antigen-specific $CD8^+$ T cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number and/or activity of antigen-specific $CD8^+$ T cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the number and/or activity of $CD8^+$ T in an individual by 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 75%, or more than 75%, compared to the number and/or activity of $CD8^+$ T in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the number and/or activity of antigen-specific $CD8^+$ T in an individual by 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 75%, or more than 75%, compared to the number and/or activity of antigen-specific $CD8^+$ T in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the number and/or activity of autoantigen-specific $CD8^+$ T cells in an individual by 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 75%, or more than 75%, compared to the number and/or activity of autoantigen-specific $CD8^+$ T cells in the individual in the absence of treatment with the immunomodulatory composition.

[0064] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of cytolytic T cells

in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of cytolytic T cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number and/or activity of cytolytic T cells in the individual in the absence of treatment with the immunomodulatory composition. In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of antigen-specific cytolytic T cells in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of antigen-specific cytolytic T cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number and/or activity of antigen-specific cytolytic T cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the number and/or activity of cytolytic T cells in an individual by 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 75%, or more than 75%, compared to the number and/or activity of cytolytic T cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the number and/or activity of antigen-specific cytolytic T cells in an individual by 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 75%, or more than 75%, compared to the number

and/or activity of antigen-specific cytolytic T cells in the individual in the absence of treatment with the immunomodulatory composition.

[0065] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate the number and/or activity of one or more of natural killer (NK) cells, NKT cells, γδ T cells, innate lymphoid cells (ILCs), macrophages, and dendritic cells (DCs) in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate the number and/or activity of one or more of NK cells, NKT cells, γδ T cells, ILCs, macrophages, and DCs in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number and/or activity of one or more of NK cells, NKT cells, γδ T cells, ILCs, macrophages, and DCs in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate the number and/or activity of one or more of NK cells, NKT cells, γδ T cells, ILCs, macrophages, and DCs in an individual by 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 75%, or more than 75%, compared to the number and/or activity of NK cells, NKT cells, γδ T cells, ILCs, macrophages, and DCs in the individual in the absence of treatment with the immunomodulatory composition.

[0066] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate the number and/or activity of regulatory cells in an individual. Regulatory T cells (Tregs) are $CD4^+$ or $CD8^+$, and may also be $FoxP3^+$. Tregs may also be defined by other markers such as PD-1, CTLA-4 etc. Regulatory cells can also be comprised of other innate cells such as NK, NKT, γδ T cells, ILCs and DCs, and B lymphocytes. NK and NKT can also be $FoxP3^+$ and may also be defined by other markers such as PD-1. "Modulate the number and/or activity" of regulatory cells, as used

herein, refers to increasing, decreasing, or balancing the number and/or activity of regulatory cells. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate the number and/or activity of regulatory cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared number and/or activity of regulatory cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to increase the number of regulatory cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number of regulatory cells in the individual in the absence of treatment with the immunomodulatory composition. As one example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to increase the number of $CD8^+$ regulatory cells (e.g., $CD8^+/CD25^+/FoxP3^+$ cells) in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number of $CD8^+$ regulatory cells (e.g., $CD8^+/CD25^+/FoxP3^+$ cells) in the individual in the absence of treatment with the immunomodulatory composition. As another example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to increase the number of $CD8^+$ regulatory cells (e.g., $CD8^+/FoxP3^+$ cells) in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold,

at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number of $CD8^+$ regulatory cells (e.g., $CD8^+/FoxP3^+$ cells) in the individual in the absence of treatment with the immunomodulatory composition As another example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to increase the number of NKT cells (e.g., $NKT^+/FoxP3^+$ cells) in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number of NKT cells (e.g., $NKT^+/FoxP3^+$ cells) in the individual in the absence of treatment with the immunomodulatory composition. As another example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to increase the number of NKT cells (e.g., $NKT^+/PD\text{-}1^+$ cells) in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number of NKT cells (e.g., $NKT^+/PD\text{-}1^+$ cells) in the individual in the absence of treatment with the immunomodulatory composition. As another example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to increase the number of NK cells (e.g., $NK^+/FoxP3^+$ cells) in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number of NK cells (e.g., $NK^+/FoxP3^+$ cells) in the individual in the absence of treatment with the immunomodulatory composition. As another example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to increase the number of NK cells (e.g., $NK^+/PD\text{-}1^+$ cells) in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number of NK cells (e.g., $NK^+/PD\text{-}1^+$ cells) in the individual in the absence of treatment with the immunomodulatory composition. As another example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to increase the number of $CD4^+$ regulatory cells (e.g., $CD4^+/FoxP3^+$ cells) in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number of $CD4^+$ regulatory cells (e.g., $CD4^+/FoxP3^+$ cells) in the individual in the absence of treatment with the immunomodulatory composition. As another example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to increase the number of $CD4^+$ regulatory cells (e.g., $CD4^+/CD25^+/FoxP3^+$ cells) in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number of $CD4^+$ regulatory cells (e.g., $CD4^+/CD25^+/FoxP3^+$ cells) in the individual in the absence of treatment with the immunomodulatory composition.

[0067] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of Th17 cells in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of Th17 cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more

than 100-fold, compared to the number and/or activity of Th17 cells in the individual in the absence of treatment with the immunomodulatory composition. In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of antigen-specific Th17 cells in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of antigen-specific Th17 cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number and/or activity of antigen-specific Th17 cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the number and/or activity of Th17 cells in an individual by 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 75%, or more than 75%, compared to the number and/or activity of Th17 cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the number and/or activity of antigen-specific Th17 cells in an individual by 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 75%, or more than 75%, compared to the number and/or activity of antigen-specific Th17 cells in the individual in the absence of treatment with the immunomodulatory composition.

[0068] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to normalize the level of one or more serum markers of pathological immune responses. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, in normalizing the level of one

or more of the serum markers (these markers include, but are not restricted to, cholesterol (CHOL), glucose (GLU), globulin (GLOB), alanine aminotransferases (ALT), aspartate aminotransferases (AST), total phosphates (TP), total bilirubin (TBIL), phosphate (PHOS), triglycerides (TRIG), uric acid (URIC), creatine kinase (CK) and urea) in an individual by 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 75%, or more than 75%, compared with the level of CH, GLU, GLOB, ALT, AST, TP, PHOS, TRIG, URIC, CK, TBIL or urea in the individual in the absence of treatment with the immunomodulatory composition.

[0069] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of Th22 cells in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of Th22 cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number and/or activity of Th22 cells in the individual in the absence of treatment with the immunomodulatory composition. In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of antigen-specific Th22 cells in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of antigen-specific Th22 cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number and/or activity of antigen-specific Th22 cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory

composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the the number and/or activity of Th22 cells in an individual by 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 75%, or more than 75%, compared to the the number and/or activity of Th22 cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the the number and/or activity of antigen-specific Th22 cells in an individual by 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 75%, or more than 75%, compared to the the number and/or activity of antigen-specific Th22 cells in the individual in the absence of treatment with the immunomodulatory composition.

[0070] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate the number and/or activity of TH9 cells in an individual. "Modulate the number and/or activity" of TH9 cells, as used herein, refers to increasing, decreasing, or balancing the number and/or activity of TH9 cells. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate the number and/or activity of TH9 cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared number and/or activity of TH9 cells in the individual in the absence of treatment with the immunomodulatory composition.

[0071] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) and/or regulate innate and/or adaptive (including both cellular and humoral) immune responses in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of innate and/or

adaptive immune cells and/or their effector functions in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number and/or activity of one or more of innate or adaptive immune cells and/or their effector functions in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the the number and/or activity of innate and/or adaptive immune cells and/or their effector functions in an individual by 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 75%, or more than 75%, compared to the the number and/or activity of innate and/or adaptive immune cells and/or their effector functions in the individual in the absence of treatment with the immunomodulatory composition.

[0072] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to induce and/or increase apoptosis in innate and/or adaptive immune cells in an individual to protect from undesirable inflammation. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to induce and/or increase apoptosis in innate and/or adaptive immune cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number of one or more of innate or adaptive immune cells in the individual in the absence of treatment with the immunomodulatory composition.

[0073] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to induce proliferation and/or differentiation of hematopoietic stem cells, and restore homeostasis. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to induce proliferation and/or

differentiation of hematopoietic stem cells, and restore homeostasis in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the individual in the absence of treatment with the immunomodulatory composition.

[0074] In some cases, an immunomodulatory composition of the present disclosure comprises CC and an antigen. Where an immunomodulatory composition of the present disclosure comprises CC and an antigen, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) an immune response to the antigen by at least about 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the immune response to the antigen in the absence of treatment with the immunomodulatory composition. For example, where the antigen is an antigen associated with or derived from an autoantigen or an allergen, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) an immune response to the antigen by at least about 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the immune response to the antigen in the absence of treatment with the immunomodulatory composition. For example, where the immunomodulatory composition comprises CC, an antigen, an autoantigen or an allergen, alone or in combination with each other, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the immune response to the antigen in an individual by 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 75%, or more than 75%, compared to the immune response to the antigen in the individual in the absence of treatment with the immunomodulatory composition.

[0075] The immune response can be a humoral immune response, e.g., a B cell or antibody immune response. Thus, e.g., in some cases, where the antigen is an antigen associated with or derived from an autoantigen or an allergen, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) a B cell response to the antigen by at least about 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the B cell response to the antigen in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the B cell response to the antigen in an individual by 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 75%, or more than 75%, compared to the B cell response to the antigen in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, where the antigen is an antigen associated with or derived from an autoantigen or an allergen, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the amount of antibody specific to the antigen by at least about 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the amount of antibody specific to the antigen in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the amount of antibody specific to the antigen in an individual by 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 75%, or more than 75%, compared to the amount of antibody specific to the antigen in the individual in the absence of treatment with the immunomodulatory composition.

[0076] The immune response can be a cellular immune response, e.g., a T cell response. Thus, e.g., in some cases, where the antigen is an antigen associated with or derived from an autoantigen or an allergen, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate a (e.g., reduce) T cell response to the antigen by at least about 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the T cell response to the antigen in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the T cell response to the antigen in an individual by 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 75%, or more than 75%, compared to the T cell response to the antigen in the individual in the absence of treatment with the immunomodulatory composition. In some cases, the immune response is a humoral immune response and a cellular immune response.

[0077] An immunomodulatory composition of the present disclosure can comprise CC in an amount of from about 10^3 CC per ml to about 10^{12} CC per ml. For example, an immunomodulatory composition of the present disclosure can comprise CC in an amount of from about 10^3 CC per ml to about 10^4 CC per ml, from about 10^4 CC per ml to about 10^5 CC per ml, from about 10^5 CC per ml to about 10^6 CC per ml, from about 10^6 CC per ml to about 10^7 CC per ml, from about 10^8 CC per ml to about 10^9 CC per ml, from about 10^9 CC per ml to about 10^{10} CC per ml, from about 10^{10} CC per ml to about 10^{11} CC per ml, or from about 10^{11} CC per ml to about 10^{12} CC per ml.

[0078] An immunomodulatory composition of the present disclosure can comprise CC in an amount of from about 10^3 CC per mg to about 10^{12} CC per mg. For example, an immunomodulatory composition of the present disclosure can comprise CC in an amount of from about 10^3 CC per mg to about 10^4 CC per mg, from about 10^4 CC per mg to about 10^5 CC per mg, from about 10^5 CC per mg to about 10^6 CC per mg, from about 10^6 CC per mg to about 10^7 CC per mg, from about 10^8 CC per mg to about 10^9 CC per mg, from about 10^9 CC per mg to about 10^{10} CC per mg, from about 10^{10} CC per mg to about 10^{11} CC per mg, or from about 10^{11} CC per mg to about 10^{12} CC per mg.

[0079] An immunomodulatory composition of the present disclosure can comprise CC in an amount of from about 10^3 CC per gram to about 10^{15} CC per gram. For example, an immunomodulatory composition of the present disclosure can comprise CC in an amount of from about 10^3 CC per gram to about 10^4 CC per gram, from about 10^4 CC per gram to about 10^5 CC per gram, from about 10^5 CC per gram to about 10^6 CC per gram, from about 10^6 CC per gram to about 10^7 CC per gram, from about 10^8 CC per gram to about 10^9 CC per gram, from about 10^9 CC per gram to about 10^{10} CC per gram, from about 10^{10} CC per gram to about 10^{11} CC per gram, from about 10^{11} CC per gram to about 10^{12} CC per gram, from about 10^{12} CC per gram to about 10^{13} CC per gram, from about 10^{13} CC per gram to about 10^{14} CC per gram, or from about 10^{14} CC per gram to about 10^{15} CC per gram.

[0080] An immunomodulatory composition of the present disclosure can comprise CC in an amount of from about 10^2 to about 10^{20} colony forming units (cfu) per unit dosage form; for example, an immunomodulatory composition of the present disclosure can comprise CC in an amount of from about 10^2 to about 10^3 from about 10^3 to about 10^5, from about 10^5 to about 10^7, from about 10^7 to about 10^9, from about 10^9 to about 10^{11}, from about 10^{11} to about 10^{13}, from about 10^{13} to about 10^{15}, from about 10^{15} to about 10^{18}, or from about 10^{18} to about 10^{20}, cfu per unit dosage form. A unit dosage form can be an amount that is administered in a single dose; for example, a unit dosage form can be 0.5 ml, 1.0 ml, or other volume suitable for administration in a single dose.

[0081] CC can be prepared by exposing *Caulobacter crescentus* to a temperature of from about 0°C to about 37°C (e.g., from about 0°C to 15°C; from about 10°C to 20°C; from about 20°C to 25°C; from about 23°C to 25°C; from about 23°C to 37°C; or from about 30°C to 35°C) for a time period of from about 1 hour to extended periods of time (e.g., at least 1 hour; at least 2 hours; at least 4 hours; overnight; at least 24 hours; at least 48 hours; at least 100 hours, or more than 100 hours). CC can also be stored in saline, phosphate-buffered saline (PBS), or any other buffer, at temperatures from about 36°C to -170°C (e.g., from about 0°C to 36°C; from about 0°C to 4°C; from about 10°C to 15°C; from about 0°C to -20°C; from about -10°C and below), or in conditions known to those skilled in the art. CC can be 0.0000001 to 100% viable. For example, CC can be 0.0000001 to 0.000001% viable, 0.000001 to 0.00001% viable, 0.00001 to 0.0001% viable, 0.0001% to 0.001% viable, 0.001% to 0.01% viable, 0.01% to 0.1% viable, 0.1% to 1% viable, 1% to 10% viable, from 10% to 100% viable, from 25% to 100 viable, from 50% to 100% viable, from 75% to 100% viable, or from 90% to 100% viable.

[0082] An immunomodulatory composition of the present disclosure can comprise CC grown in culture at various optical density units (ODs) from about 0.1 OD to 30.0 ODs. For example, the OD of the CC culture grown can be 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 etc.

Caulobacter crescentus

[0083] An immunomodulatory composition of the present disclosure comprises *Caulobacter*, where the Caulobacter is non-pathogenic. The non-pathogenic Caulobacter genus includes 19 different species, including two species of Asticcacaulis (C. vibroides, C. henricii, C. intermedius, C. robiginosus, C. rutilis, C. subvibriodes, C. fusiformis, C. rossii, A. excentricus, A. biprosthecum etc.). See, e.g., JS Poindexter, The Caulobacters: Ubiquitous Unusual Bacteria, Microbiol Rev 45, 123-179, 1981). Several of the Caulobacter sp. are available from the American Type Culture Collection (ATCC), such as CB35, CB26, CB28, KA5, CB66, FC4 etc. All of these species of Caulobacter in live, non-denatured, mutated or attenuated forms can be used as immunomodulatory agents described herein. In addition, Caulobacter bacteria can be in non-motile prosthecate, motile swarmer, stubby flagellin and flagellin positive, flagellin negative, dividing and/or non-dividing forms. Caulobacter sp. can be grown at temperatures ranging from 18° – 42° C, and pH ranging from 5-9, but optimally at a temperature in a range of 23-25° C and pH 7 in PYE medium. Mutated or genetically modified forms of Caulobacter sp. can be produced by modifying the nutrients, chemicals, pH, temperature, ultraviolet or infrared light, radiation etc. of the culture conditions, or genetically modifying various enzymes, metabolic pathways, surface molecules, nucleic acids, plasmids, cellular and cell wall components, smooth and rough LPS in live bacteria (JS Poindexter, The Caulobacters: Ubiquitous Unusual Bacteria, Microbiol Rev 45, 123-179, 1981).

[0084] *Caulobacter crescentus* can act as a carrier and/or delivery vehicle to deliver antigens. As a non genetic modification (GM), such as electrostatic and hydrophobic interactions, binding of antigens to the *Caulobacter crescentus* surface may enable the *Caulobacter crescentus* to act as an antigen carrier and/or delivery vehicle. Further, due to bioadhesion/mucoadhesion, *Caulobacter crescentus* may facilitate antigen uptake by M cell transport, delivery to and subsequent modulation of DCs/APCs, modulation of NK, NKT, B and T cell responses at mucosal surfaces.

[0085] Although the discussion below focuses on *Caulobacter crescentus*, any of a variety of non-pathogenic Caulobacter species can be included in an immunomodulatory composition of the present disclosure.

[0086] In some cases, an immunomodulatory composition of the present disclosure comprises *Caulobacter crescentus* (CC). In some cases, the *Caulobacter crescentus* is wild-type. In some cases, the *Caulobacter crescentus* is a lipopolysaccharide-negative strain. In some cases, the *Caulobacter crescentus* is an S-layer-negative strain. In some cases, the CC is mutated attenuated, or contains suicidal mutations. In some cases, *Caulobacter crescentus* is with or without a drug resistant plasmid such as chloramphenicol, penicillin resistant plasmids. In some cases, *Caulobacter crescentus* can be grown in other medium than PYE medium.

[0087] In some cases, the *Caulobacter crescentus* is genetically modified to produce one or more heterologous polypeptides. The polypeptides can be of a wide range of sizes. Suitable heterologous polypeptides include, but are not limited to, PD1, PDL, CTLA-4, GITR, VISTA; a co-inhibitory protein found on antigen-presenting cells (APCs) or T cells; a cytokine (e.g., IL-10; or any of the above-listed cytokines); a chemokine; an antigen (e.g., an autoantigen or allergen as described herein above); an antibody against an antigen (e.g., an autoantigen; as described herein above), a signalling molecule, a receptor, a cytokine, a pro-apoptotic protein; a fusion protein (e.g., an antigen and a cytokine, an antigen and a carrier protein) etc.

[0088] In some cases, *Caulobacter crescentus* is modified by labeling or coupling the bacterium with fluorescent, radioactive isotope, light tags etc.

[0089] In some cases, *Caulobacter crescentus* is genetically modified. In some cases, *Caulobacter crescentus* is genetically modified so that microbe is attenuated. In some cases, the nucleic acid of the *Caulobacter crescentus* is modified so that the microbe is attenuated for proliferation.

[0090] In some cases, an immunomodulatory composition of the present disclosure comprises whole CC. In some cases, an immunomodulatory composition of the present disclosure comprises CC that are live or non-denatured. In some cases, an immunomodulatory composition of the present disclosure comprises individual or multiple components, byproducts and/or metabolites of CC, which can be isolated, synthesized, or genetically manufactured in other synthetic or natural bacterial cell as synthetic biotics. The components of CC can comprise, but are not limited to, effector molecules e.g., polysaccharides, glycosylceramides, peptidoglycans, nucleic acids, structural proteins, short chain fatty acids, fatty acid metabolites, hydroxyl fatty acids etc. Fractions, components, by-products and/or metabolites of *Caulobacter crescentus* can be obtained by filtering culture supernatants, treatment with various organic solvents, enzymes such

as glycosidases, lipase, DNAse, RNAse, protease, lysozyme etc. In some cases, an immunomodulatory composition of the present disclosure comprises individual or multiple components of CC, which can be fused with antigens using physicochemical or genetic methods and used as synthetic bacteria.

[0091] In some cases, *Caulobacter crescentus* is bioengineered in its outer membrane vesicle to package and deliver chemotherapeutics and/or immunotherapeutics and synthetic, genetic material from other bacteria. In some cases, *Caulobacter crescentus* is bioengineered and constructed into a genetic circuit as a synthetic therapeutic bacteria, "synthetic biotics".

[0092] In some cases, an immunomodulatory composition of the present disclosure comprises S-layer of CC. In some cases, an immunomodulatory composition of the present disclosure comprises S-layer of CC that is genetically modified to display one or more heterologous polypeptides, chemotherapeutics and/or immunotherapeutics. In some cases, an immunomodulatory composition of the present disclosure comprises components of S-layer.

Antigens

[0093] An immunomodulatory composition of the present disclosure can comprise, in addition to CC, one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more than 10) antigens. Suitable antigens include, but are not limited to, an antigen derived from an autoantigen; and an allergen.

[0094] In some embodiments, *Caulobacter crescentus* is genetically modified to produce an antigen; and the genetically modified *Caulobacter crescentus* is live, to produce an immunomodulatory composition of the present disclosure. Methods of genetically modifying bacteria are known in the art.

[0095] In other embodiments, CC is admixed with an antigen in an immunomodulatory composition of the present disclosure. *Caulobacter crescentus* can act as a carrier and/or delivery vehicle to deliver antigens. As a non genetic modification (GM), such as electrostatic and hydrophobic interactions, binding of antigens to the *Caulobacter crescentus* surface may enable the *Caulobacter crescentus* to act as an antigen carrier and/or delivery vehicle. Further, due to bioadhesion/mucoadhesion, *Caulobacter crescentus* may facilitate antigen uptake by M cell transport, delivery to and subsequent modulation of DCs/APCs, modulation of NK, NKT, B and T cell responses at mucosal surfaces.

[0096] An antigen, for use in certain embodiments of the herein described immunomodulatory compositions and methods employing CC, may be any target epitope, molecule,

molecular complex, cell or tissue against which modulation of immunogenicity in a subject is desired.

[0097] An immunomodulatory composition of the present disclosure can include one or more antigens or antigenic compositions capable of modulating an immune response against a human or animal autoantigen or allergen. The antigen may be associated with autoimmune disease, allergy, asthma, prion disease or any other conditions where modulation of an antigen-specific response would be desirable or beneficial.

[0098] A suitable antigen can be any type of antigen known in the art. Antigens can be produced in any of a variety of sources such as plants, animals, prokaryotes, *in vitro* cell culture, etc. Antigens can be in variety of forms as described below.

[0099] Suitable antigens include, e.g., peptides, modified peptides, peptide mimotopes, conformationally-constrained synthetic peptides, multi-epitope peptides from one or more antigens, branched peptides, lipopeptides, monolipopeptides, dilipopeptides, peptides conjugated or fused to proteins, peptides conjugated or fused to T cell or B cell epitopes. See, e.g., U.S. Patent No. 8,198,400. Suitable antigens include, e.g., full-length antigens, truncated antigens, mutated antigens, and inactivated or combined forms. Suitable antigens include, e.g., proteins, purified or recombinant proteins, recombinant fusion proteins, proteins and peptides conjugated to toll-like receptor (TLR) agonists/antagonists, proteins and peptides conjugated to bacterial toxins, proteins and peptides conjugated to antibodies, proteins and peptides conjugated to cytokines and chemokines, glycoproteins, glycolipoproteins and derivatives thereof. Suitable antigens include, e.g., polysaccharides, polysaccharide conjugates, oligosaccharides, lipids, glycolipids, carbohydrates and derivatives thereof.. An antigen can be modified to modulate antigen presentation and/or co-inhibition, or increase co-inhibitory signals.

[00100] An antigen or antigenic composition can be obtained from autoantigens, allergens, etc.

[00101] An antigen can be a whole cell extract, a cell lysates, a whole cell, a whole live cell, a whole inactivated cell, a whole irradiated cell, etc. Antigens may be crude, purified, or recombinant form. In some cases, an antigen is at least 50% pure, at least 60% pure, at least 70% pure, at least 80% pure, at least 90% pure, at least 95% pure, at least 98% pure, or at least 99% pure, or more than 99% pure.

[00102] An antigen can be chemically, enzymatically, or genetically coupled to CC. In some cases, an antigen is present in an immunomodulatory composition of the present disclosure in admixture with CC.

[00103] An immunomodulatory composition of the present disclosure can comprise a single type of antigen. An immunomodulatory composition of the present disclosure can include 2 or more different antigens. An immunomodulatory composition of the present disclosure can include 2, 3, 4, 5, 6, or more than 6, different antigens. Where an immunomodulatory composition of the present disclosure includes more than one antigen, the more than one antigen can be from the same cell or allergen. Where an immunomodulatory composition of the present disclosure includes more than one antigen, the more than one antigen can be from two or more cells, or allergens.

[00104] An antigen can be in the form of a protein, a lipopolysaccharide, a lipoprotein, a proteoglycan, glycoproteins, glycosaminoglycans, an oligosaccharide, etc.

[00105] An antigen can be in the form of a nucleic acid comprising a nucleotide sequence encoding an antigen, e.g., a polypeptide antigen. For example, an antigen can be provided in the form of DNA (e.g., plasmid DNA, naked DNA etc.), RNA, and/or a wild-type, attenuated and/or recombinant vector-based nucleic acid. The nucleic acid coding for the antigen can be either "naked" or contained in a delivery system, such as liposomes.

[00106] A recombinant vector-encoded antigen can be at least one recombinant expression construct which comprises a promoter operably linked to a nucleotide sequence encoding an antigen in recombinant viral vectors (such as adenovirus (e.g. Ad2, Ad4, Ad5, Ad35, Ad35K5 etc.), adeno-associated virus, lentivirus, herpes virus, poxvirus, vesicular stomatitis virus, alpha virus, measles virus, papaya mosaic virus, cytomegalovoirus, modified vaccinia Ankara virus MVA, polio virus, Marba virus etc.), bacterial vector vaccines (such as Salmonella, Shigella, E. coli, Lactococcus lactis, Listeria sp., Lactobacillus sp.), fungal vectors (such as heat killed recombinant Saccharomyces yeast), plant viruses, virus-like particles (VLPs), virosomes, synthetic vaccine particles, synthetic biomimetic supramolecular biovectors, depathogenized viral/bacterial strains (such as NIBRG14 from H5N1). The vector could be in the form of live wild-type, non-replicative, mutated, modified, defective or attenuated. The vectors could be from human, animal, plant or prokaryote origin and in any effective amount.

[00107] In treating or preventing autoimmune diseases or allergy, antigen can be given at the same or different times, at the same or different site than the immunomodulatory composition of the present disclosure.

Autoantigens

[00108] In some cases, an immunomodulatory composition of the present disclosure comprises, in addition to CC, an autoantigen. In some cases, an immunomodulatory

composition of the present disclosure comprises, in addition to CC, one or more autoantigens, e.g., 1, 2, 3, 4, 5, or more antigens, from one or more self tissues.

[00109] For example, where the autoimmune disease is type 1 diabetes, an antigen can be pancreatic islet beta cell associated antigen, proinsulin, glutamic acid decarboxylase, chromogranin A, islet amyloid polypeptide, HSP60; for systemic lupus erythematosus, an antigen can be snRNP; for Grave's disease, an antigen can be thyroglobulin, thyrotropin receptor or a thyroid epithelial cell; for thrombocytopenic purpura, an antigen can be a platelet, GPIIB/IIIa; for multiple sclerosis, an antigen can be myelin basic protein, MOG, PLP; for celiac disease, an antigen can be transglutaminidase.

[00110] A suitable autoantigen can be an autoantigen involved in the initiation and/or propagation of an autoimmune disease, the pathology of which can be due to the presence of antibodies specific for a molecule expressed by the relevant target organ, tissue, or cells, e.g., systemic lupus erythematosus (SLE) or myasthenia gravis (MG). In such diseases, it can be desirable to direct an ongoing antibody-mediated (i.e., a Th2-type) immune response to the relevant autoantigen towards a cellular (i.e., a Th1-type) immune response. Alternatively, it can be desirable to prevent onset of or decrease the level of a Th2 response to the autoantigen in a subject not having, but who is suspected of being susceptible to, the relevant autoimmune disease by prophylactically inducing a Th1 response to the appropriate autoantigen. Autoantigens that can be included in a subject immunomodulatory composition include, without limitation: (a) with respect to SLE, the Smith protein, RNP ribonucleoprotein, and the SS-A and SS-B proteins; and (b) with respect to MG, the acetylcholine receptor. Examples of other antigens involved in one or more types of autoimmune response include, e.g., endogenous hormones such as luteinizing hormone, follicular stimulating hormone, testosterone, growth hormone, prolactin, and other hormones.

[00111] Other examples of suitable autoantigens include antigens associated with neurological diseases such as schizophrenia, Alzheimer's disease, depression, hypopituitarism, and cardiovascular diseases such as atherosclerosis (e.g., an antigen for atherosclerosis can be cholesteryl ester transfer protein, oxidized LDL, apoB210, apoB100) etc.

[00112] Those of skill in the art will recognize that other suitable autoantigens include those that are associated with juvenile rheumatoid arthritis and Marie-Strumpell ankylosing spondylitis, that can lead to anterior uveitis and subsequent glaucoma. Other

suitable autoantigens include those that are associated with Huntington's disease, and Parkinson's disease.

[00113] Examples of autoantigens include those that are associated with cell or organ-specific autoimmunity. Such autoantigens include the acetylcholine receptor, associated with Myasthenia gravis; actin, associated with chronic active hepatitis and primary biliary cirrhosis; adenine nucleotide translocator (ANT), associated with dilated cardiomyopathy and myocarditis; β-adrenoreceptor, associated with dilated cardiomyopathy; aromatic L-amino acid decarboxylase, associated with autoimmune polyendocrine syndrome type I (APS-I); asialoglycoprotein receptor, associated with autoimmune hepatisis; bactericidal/permeability-increasing protein (Bpi), associated with cystic fibrosis vasculitides; calcium-sensing receptor, associated with acquired hypoparathryoidism; cholesterol side-chain cleavage enzyme (CYPIIa), associated with APS-I; collagen type IV α_3-chain; associated with Goodpasture syndrome; cytochrome P450 2D6 (CYP2D6), associated with autoimmune hepatisis; desmin, associated with Crohn disease and coronary artery disease; desmoglein 1, associated with pemphigus foliaceus; desmoglein 3, associated with pemphigus vulgaris; F-actin, associated with autoimmune hepatitis; GM gangliosides, associated with Guillain-Barré syndrome; glutamate decarboxylase (GAD65), associated with type 1 diabetes and stiff man syndrome; glutamate receptor (GLUR), associated with Rasmussen encephalitis; H/K ATPase, associated with autoimmune gastritis; 17-α-hydroxylase (CYP17), associated with APS-I; 21-hydroxylast (CYP21), associated with Addison disease; IA-2 (ICA512), associated with type 1 diabetes; insulin, associated with type 1 diabetes and insulin hypoglycemic syndrome (Hirata disease); insulin receptor, associated with type B insulin resistance, acanthosis and systemic lupus erythematosus (SLE); intrinsic factor type 1, associated with pernicious anemia, leukocyte function-associated antigen (LFA-1), associated with treatment-resistant Lyme arthritis; myelin-associated glycoprotein (MAG), associated with polyneuropathy; myelin basic protein, associated with multiple sclerosis and demyelinating diseases; myelin oligodendrocyte glycoprotein (MOG), associated with multiple sclerosis; myosis, associated with rheumatic fever; p-80-coilin, associated with atopic dermatitis; pyruvate dehydrogenase complex-E2 (PDC-E2), associated with primary biliary cirrhosis; sodium iodid symporter (NIS), associated with Graves disease and autoimmune hypothyroidism; SOX-10, associated with vitiligo; thyroid and eye muscle shared protein, associated with thyroid associated ophthalmopathy; thyroglobulin, associated with autoimmune thyroiditis; thyroid peroxidase, associated with autoimmune

Hashimoto thyroiditis; thyrotropin receptor, associated with Graves disease; tissue transglutaminase, associated with coeliac disease; transcription coactivator p75, associated with atopic dermatitis; tryptophan hydroxylase, associated with APS-I; tyrosinase, associated with vitiligo and metastatic melanoma; and tyrosine hydroxylase, associated with APS-I.

[00114] Examples of autoantigens include those that are associated with systemic autoimmunity. Such autoantigens include ACTH, associated with ACTH deficiency; aminoacyl-tRNA histidyl synthetase, associated with myotitis and dermatomyositis; aminoacyl-tRNA synthetase (several), associated with polymyositis and dermatomyositis; cardiolipin, associated with SLE; carbonic anhydrase II, associated with SLE, Sjögren syndrome and systemic sclerosis; collagen (multiple types), associated with rheumatoid arthritis (RA), SLE and progressive systemic sclerosis; centromere-associated proteins, associated with systemic sclerosis; DNA-dependent nucleosome-stimulated ATPase, associated with dermatomyositis; fibrillarin, associated with scleroderma; fibronectin, associated with SLE, RA and morphea; glucose-6-phosphate isomerase, associated with RA; β2-glycoprotein I (β2-GPI), associated with primary antiphospholipid syndrome; golgin (95, 97, 160, 180), associated with Sjögren syndrome, SLE and RA; heat shock protein, associated with various immune-related disorders; hemidesmosomal protein 180, associated with bullous pemphigoid, herpes gestationis and cicatricial pemphigoid; histone H2A-H2B-DNA, associated with SLE; IgE receptor, associated with chronic idiopathic urticaria; keratin, associated with RA; Ku-DNA-protein kinase, associated with SLE; Ku-nucleoprotein, associated with connective tissue syndromes; La phosphoprotein (La 55-B), associated with Sjögren syndrome; myeloperoxidase, associated with necrotizing and crescentic glomerulonephritis and systemic vasculitis; proteinase 3 (PR3), associated with Wegener granulomatosis and Churg-Strauss syndrome; RNA polymerase I-III (RNP), associated with systemic sclerosis and SLE; signal recognition protein (SRP54), associated with polymyositis; topoisomerase-I (Scl-70), associated with scleroderma and Raynaud syndrome; tubulin, associated with chronic liver disease and visceral leishmaniasis; and vimentin, associated with systemic autoimmune disease.

[00115] Other examples of autoantigens include those that are associated with plasma protein and cytokine autoimmunity. Such autoantigens include C1 inhibitor, associated with autoimmune C1 deficiency; C1q, associated with SLE and membrane proliferative glomerulonephritis (MPGN); cytokines (IL-1α, IL-1β, IL-6, IL-10, LIF), associated with

RA and systemic sclerosis; factor II, factor V, factor VII, factor VIII, factor IX, factor X, factor XI, factor XII, thrombin, vWF, associated with prolonged coagulation time; glycoprotein IIb/IIIg and 1B/IX, associated with autoimmune thrombocytopenia purpura; IgA, associated with immunodeficiency; and oxidized LDL (OxLDL), associated with artherosclerosis.

[00116] Yet more examples of autoantigens include those that are associated with cancer and paraneoplastic autoimmunity. Such autoantigens include amphiphysin, associated with neuronopathy and small lung cell cancer; cyclin B1, associated with hepatocellular carcinoma; DNA topoisomerase II, associated with liver cancer; desmoplakin, associated with paraneoplastic pemphigus; gephyrin, associated with paraneoplastic stiff man syndrome; Hu proteins, associated with paraneoplastic encephalomyelitis; neuronal nicotinic acetylcholine receptor, associated with subacute autonomic neuropathy and cancer; p53, associated with cancer and SLE; p62 (IGF-II mRNA-binding protein), associated with hepatocellular carcinoma (China); recoverin, associated with cancer-associated retinopathy; Ri protein, associated with paraneoplastic opsoclonus myoclonus ataxia; β IV spectrin, associated with lower motor neuron syndrome; synaptotagmin, associated with Lambert-Eaton myasthenic syndrome; voltage-gated calcium channels, associated with Lamber-Eaton myasthenic syndrome; and Yo protein, associated with paraneoplastic cerebellar degeneration.

Allergens

[00117] In some cases, an immunomodulatory composition of the present disclosure comprises, in addition to CC, an allergen. Suitable allergens can be obtained and/or produced using known methods. Classes of suitable allergens include, but are not limited to, pollens, animal dander other than cat dander, grasses, molds, dusts, antibiotics, stinging insect venoms, and a variety of environmental (including chemicals and metals), drug and food allergens. Common tree allergens include pollens from cottonwood, popular, ash, birch, maple, oak, elm, hickory, and pecan trees; common plant allergens include those from mugwort, ragweed, English plantain, sorrel-dock and pigweed; plant contact allergens include those from poison oak, poison ivy and nettles; common grass allergens include rye grass, Timothy, Johnson, Bermuda, fescue and bluegrass allergens; common allergens can also be obtained from molds or fungi such as Alternaria, Fusarium, Hormodendrum, Aspergillus, Micropolyspora, Mucor and thermophilic actinomycetes; epidermal allergens can be obtained from house or organic dusts (typically fungal in origin), from arthropods such as house mites (Dermatophagoides

pteronyssinus), or from animal sources such as feathers, and dog dander; common food allergens include milk and cheese (diary), egg, wheat, nut (e.g., peanut), seafood (e.g., shellfish), pea, bean and gluten allergens; common environmental allergens include metals (nickel and gold), chemicals (formaldehyde, trinitrophenol and turpentine), Latex, rubber, fiber (cotton or wool), burlap, hair dye, cosmetic, detergent and perfume allergens; common drug allergens include local anesthetic and salicylate allergens; antibiotic allergens include penicillin, tetracycline and sulfonamide allergens; and common insect allergens include bee, wasp and ant venom, and cockroach calyx allergens. Particularly well characterized allergens include, but are not limited to, the major and cryptic epitopes of the Der p I allergen (Hoyne et al. (1994) Immunology 83190-195), bee venom phospholipase A2 (PLA) (Akdis et al. (1996) J. Clin. Invest. 98:1676-1683), birch pollen allergen Bet v 1 (Bauer et al. (1997) Clin. Exp. Immunol. 107:536-541), and the multi-epitopic recombinant grass allergen rKBG8.3 (Cao et al. (1997) Immunology 90:46-51). These and other suitable allergens are commercially available and/or can be readily prepared as extracts following known techniques.

[00118] Suitable allergens include tree pollen allergens, weed pollen allergens, herb pollen allergens, grass pollen allergens, mite allergens, insect allergens, venom allergens, animal hair allergens, dander allergens and food allergens.

[00119] In some cases, the allergen is in the form of an extract, a purified allergen, a modified allergen or a recombinant allergen or a mutant of a recombinant allergen or any combination thereof. In some cases, the allergen is selected from the group consisting of grass pollen allergen, dust mite allergen, ragweed allergen, cat allergen and birch allergen.

[00120] An allergen can be present in an immunomodulatory composition of the present disclosure in an amount of from about 2.5 μg to about 75 μg per unit dosage form. For example, an allergen can be present in an immunomodulatory composition of the present disclosure in an amount of from about 2.5 μg to about 5 μg, from about 5 μg to about 10 μg, from about 10 μg to about 15 μg, from about 15 μg to about 20 μg, from about 20 μg to about 25 μg, from about 25 μg to about 50 μg, or from about 50 μg to about 75 μg, or more than 75 μg, per unit dosage form.

[00121] In some cases, a dose of an immunomodulatory composition of the present disclosure that comprises an allergen has a potency of about 65 to about 17,600 Biological Allergen Units (BAU). In some cases, a dose of an immunomodulatory

composition of the present disclosure that comprises an allergen comprises from about 650 BAU to about 6,000 BAU.

Antibodies

[00122] In some cases, an immunomodulatory composition of the present disclosure comprises, in addition to CC, an antibody against a cancer antigen, an autoantigen, an allergen or a pathogenic antigen (e.g., a therapeutic antibody, monoclonal antibodies, bispecific antibodies, chemoimmuno conjugated antibodies, radioimmunoconjugated antibodies, antibody-cytokine fusion proteins, antibody-antigen fusion proteins, antibody-immunotoxin fusion protein etc.).

[00123] Antibodies that can be included in an immunomodulatory composition of the present disclosure include, without limitation, antibodies directed against co-stimulatory or co-inhibitory molecules (CD28, CD40, CTLA-4, PD-1, PDL-1, GITR, VISTA, LAG-3, ICOS, CD137, OX40, CD137, CD227, CTLA-4, KIRs, TCR, TIM3etc.); and other therapeutic antibodies.

[00124] Non-limiting examples of suitable antibodies include, but are not limited to, adalimumab, bevacizumab, infliximab, abciximab, alemtuzumab, bapineuzumab, basiliximab, belimumab, briakinumab, brodalumab, canakinumab, certolizumab pegol, cetuximab, conatumumab, denosumab, eculizumab, etrolizumab, gemtuzumab ozogamicin, golimumab, ibritumomab tiuxetan, labetuzumab, mapatumumab, matuzumab, mepolizumab, motavizumab, muromonab-CD3, natalizumab, nimotuzumab, ofatumumab, omalizumab, oregovomab, palivizumab, panitumumab, pemtumornab, pertuzumab, ranibizumab, rituximab, rovelizumab, tocilizumab, tositumomab, trastuzumab, ustekinumab, vedolizomab, zalutumumab, and zanolimumab.

[00125] Non-limiting examples of therapeutic and prophylactic antibodies that can be used in combination with an immunomodulatory composition of the present disclosure include MDX-010 (Medarex, N.J.) which is a humanized anti-CTLA-4 antibody for the treatment of prostate cancer; SYNAGIS™ (MedImmune, Md.) which is a humanized anti-respiratory syncytial virus (RSV) monoclonal antibody for the treatment of RSV infection; and HERCEPTIN™ (Trastuzumab) (Genentech, Calif.) which is a humanized anti-HER2 monoclonal antibody for the treatment of metastatic breast cancer. Other examples are humanized anti-CD18 $F(ab')_2$ (Genentech); CDP860 which is a humanized anti-CD18 $F(ab')_2$ (Celltech, UK); PRO542 which is an anti-HIV gp120 antibody fused with CD4 (Progenics/Genzyme Transgenics); Ostavir which is a human anti-Hepatitis B virus antibody (Protein Design Lab/Novartis); PROTOVIR™ which is a humanized anti-

CMV IgGI antibody (Protein Design Lab/Novartis); MAK-195 (SEGARD) which is a murine anti-TNF-α $F(ab')_2$ (Knoll Pharma/BASF); IC14 which is an anti-CD14 antibody (ICOS Pharm); a humanized anti-VEGF IgG1 antibody (Genentech); OVAREX™ which is a murine anti-CA 125 antibody (Altarex); PANOREX™ which is a murine anti-17-IA cell surface antigen IgG2a antibody (Glaxo Wellcome/Centocor); BEC2 which is a murine anti-idiotype (GD3 epitope) IgG antibody (ImClone System); IMC-C225 which is a chimeric anti-EGFR IgG antibody (ImClone System); VITAXIN™ which is a humanized anti-αVβ3 integrin antibody (Applied Molecular Evolution/MedImmune); Campath 1H/LDP-03 which is a humanized anti-CD52 IgG1 antibody (Leukosite); Smart M195 which is a humanized anti-CD33 IgG antibody (Protein Design Lab/Kanebo); RITUXAN™ which is a chimeric anti-CD20 IgG1 antibody (IDEC Pharm/Genentech, Roche/Zettyaku); LYMPHOCIDE™ which is a humanized anti-CD22 IgG antibody (Immunomedics); Smart ID10 which is a humanized anti-HLA antibody (Protein Design Lab); ONCOLYM™ (Lym-1) is a radiolabelled murine anti-HLA DIAGNOSTIC REAGENT antibody (Techniclone); ABX-IL8 is a human anti-IL8 antibody (Abgenix); anti-CD11a is a humanized IgG1 antibody (Genentech/Xoma); ICM3 is a humanized anti-ICAM3 antibody (ICOS Pharm); IDEC-114 is a primatized anti-CD80 antibody (IDEC Pharm/Mitsubishi); ZEVALIN™ is a radiolabelled murine anti-CD20 antibody (IDEC/Schering AG); IDEC-131 is a humanized anti-CD40L antibody (IDEC/Eisai); IDEC-151 is a primatized anti-CD4 antibody (IDEC); IDEC-152 is a primatized anti-CD23 antibody (IDEC/Seikagaku); SMART anti-CD3 is a humanized anti-CD3 IgG (Protein Design Lab); 5G1.1 is a humanized anti-complement factor 5 (C5) antibody (Alexion Pharm); D2E7 is a humanized anti-TNF-α antibody (CAT/BASF); CDP870 is a humanized anti-TNF-α Fab fragment (Celltech); IDEC-151 is a primatized anti-CD4 IgG1 antibody (IDEC Pharm/SmithKline Beecham); MDX-CD4 is a human anti-CD4 IgG antibody (Medarex/Eisai/Genmab); CDP571 is a humanized anti-TNF-α IgG4 antibody (Celltech); LDP-02 is a humanized anti-α4β7 antibody (LeukoSite/Genentech); OrthoClone OKT4A is a humanized anti-CD4 IgG antibody (Ortho Biotech); ANTOVA™ is a humanized anti-CD40L IgG antibody (Biogen); ANTEGREN™ is a humanized anti-VLA-4 IgG antibody (Elan); MDX-33 is a human anti-CD64 (FcγR) antibody (Medarex/Centeon); SCH55700 is a humanized anti-IL-5 IgG4 antibody (Celltech/Schering); SB-240563 and SB-240683 are humanized anti-IL-5 and IL-4 antibodies, respectively, (SmithKline Beecham); rhuMab-E25 is a humanized anti-IgE IgG1 antibody (Genentech/Norvartis/Tanox Biosystems); ABX-CBL is a murine anti

CD-147 IgM antibody (Abgenix); BTI-322 is a rat anti-CD2 IgG antibody (MedImmune/Bio Transplant); Orthoclone/OKT3 is a murine anti-CD3 IgG2a antibody (ortho Biotech); SIMULECT™ is a chimeric anti-CD25 IgG1 antibody (Novartis Pharm); LDP-01 is a humanized anti-β_2-integrin IgG antibody (LeukoSite); Anti-LFA-1 is a murine anti CD18 F(ab')$_2$ (Pasteur-Merieux/Immunotech); CAT-152 is a human anti-TGF-β_2 antibody (Cambridge Ab Tech); and Corsevin M is a chimeric anti-Factor VII antibody (Centocor). The above-listed immunoreactive reagents, as well as any other immunoreactive reagents, may be administered according to any regimen known to those of skill in the art, including the regimens recommended by the suppliers of the immunoreactive reagents.

[00126] Other examples of therapeutic and prophylactic antibodies that can be used in combination with an immunomodulatory composition of the present disclosure include Humira and Remicade; ACTEMRA™ (Genentech) which is a recombinant monoclonal IgG1 anti-human interleukin 6-receptor antibody for the treatment of anti-TNF resistant rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA); ARZERRA™ (GlaxoSmithKline/Novartis) which is a chimeric human monoclonal antibody directed against membrane proximal epitope on the CD20 molecule for the treatment of RA; BENLYSTA™ (GlaxoSmithKline) which is a human monoclonal IgG1 gamma that binds to and inhibits the soluble form of the B-lymphocyte stimulator (BLyS) protein for the treatment of SLE; ORENCIA™ (Bristol-Myers Squibb) which is a CTLA-4 IgG1 binding to CD80/86 on antigen-presenting cells inhibiting the co-stimulation of CD28 on the T cells for the treatment of RA, JIA and SLE; SIMPONI (Janssen) which is a IgG1 monoclonal antibody acting on both soluble and membrane-bound TNF-α for the treatment of RA, psoriatic arthritis (PsA) and ankylosing spondylitis (AS); CIMZIA™ (UCB Group) which is a pegylated humanized antibody Fab' fragment of the TNF-α monoclonal antibody for the treatment of RA; Sifalimumab (MedImmune) which is an anti-IFN-α monoclonal antibody designed for the treatment of SLE, dematomyositis and polymyositis; various intravenous immunoglobulin products which are pools of immunoglobulins from healthy individuals for the treatment of SLE, systemic sclerosis and vasculitis; KINERET™ (Swedish Oprhan Biovitrum AB), ILARIS™ (Novartis) and ARCALYST™ (Regeneron) which are interleukin-1 blockers for the treatment of RA and cryopyrin-associated periodic syndrome (CAPS).

Cytokines

[00127] In some cases, an immunomodulatory composition of the present disclosure comprises, in addition to CC, a cytokine. Cytokines that can be included in an immunomodulatory composition of the present disclosure include, without limitation, interleukins, transforming growth factors (TGFs), fibroblast growth factors (FGFs), platelet derived growth factors (PDGFs), epidermal growth factors (EGFs), colony stimulating factors (CSFs), connective tissue activated peptides (CTAPs), osteogenic factors, and biologically active analogs, fragments, and derivatives of such growth factors. Suitable cytokines include B/T-cell differentiation factors, B/T-cell growth factors, mitogenic cytokines, chemotactic cytokines, colony stimulating factors, angiogenesis factors, IFN-α, IFN-β, IFN-γ, IL1, IL2, IL3, IL4, IL5, IL6, IL7, IL8, IL9, IL10, IL11, IL12, IL13, IL14, IL15, IL16, IL17, IL18, IL22, etc., leptin, myostatin, macrophage stimulating protein, platelet-derived growth factor, tumor necrosis factor (TNF)-alpha (TNF-α), TNF-β, nerve growth factor (NGF), CD40L, CD137L/4-1BBL, human lymphotoxin-β, G-CSF, M-CSF, GM-CSF, platelet-derived growth factor (PDGF), IL-1α, IL1-β, IP-10, PF4, GRO, 9E3, erythropoietin, endostatin, angiostatin, vascular endothelial growth factor (VEGF) or any fragments or combinations thereof. Other cytokines include members of the transforming growth factor (TGF) supergene family include the beta transforming growth factors (for example TGF-β1, TGF-β2, TGF-β3); bone morphogenetic proteins (for example, BMP-1, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, BMP-9); heparin-binding growth factors (for example, fibroblast growth factor (FGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF)); hematopoietic growth factors (Flt3); pituitary growth hormones or derivatives; growth hormones, neuroactive hormones, Inhibins (for example, Inhibin A, Inhibin B); differentiation factors (for example, GDF-1); and Activins (for example, Activin A, Activin B, Activin AB). In some cases, an immunomodulatory composition of the present disclosure comprises, in addition to CC, a compound or agent modulating cytokines.

Adjuvants

[00128] An immunomodulatory composition of the present disclosure can comprise, in addition to CC, one or more adjuvants.

[00129] Exemplary adjuvants include, but are not limited to: (1) oil-in-water emulsion formulations (with or without other specific immunostimulating agents such as muramyl peptides (see below) or bacterial cell wall components), such as for example (a) MF59™

(WO 90/14837; Chapter 10 in Vaccine design: the subunit and adjuvant approach, eds. Powell & Newman, Plenum Press 1995), containing 5% Squalene, 0.5% Tween 80, and 0.5% Span 85 (optionally containing MTP-PE) formulated into submicron particles using a microfluidizer, (b) SAF, containing 10% Squalane, 0.4% Tween 80, 5% pluronic-blocked polymer L121, and thr-MDP either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion, and (c) RIBI™ adjuvant system (RAS), (Ribi Immunochem, Hamilton, Mont.) containing 2% Squalene, 0.2% Tween 80, and one or more bacterial cell wall components such as monophosphorylipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), e.g., MPL+CWS (Detox™); (2) saponin adjuvants, such as QS21 or Stimulon™(Cambridge Bioscience, Worcester, Mass.) may be used or particles generated therefrom such as ISCOMs (immunostimulating complexes), which ISCOMS may be devoid of additional detergent e.g. WO 00/07621; (3) Complete Freund's Adjuvant (CFA) and Incomplete Freund's Adjuvant (IFA); (4) cytokines, such as interleukins (e.g. IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12, IL-15, IL-28, etc.) (WO99/44636), etc.), interferons (e.g. gamma interferon), macrophage colony stimulating factor (M-CSF), tumor necrosis factor (TNF), colony-stimulating factors (e.g., GM-CSF), etc.; (5) monophosphoryl lipid A (MPL) or 3-O-deacylated MPL (3dMPL) e.g. GB-2220221, EP-A-0689454, optionally in the substantial absence of alum when used with pneumococcal saccharides e.g. WO 00/56358; (6) combinations of 3dMPL with, for example, QS21 and/or oil-in-water emulsions e.g. EP-A-0835318, EP-A-0735898, EP-A-0761231; (7) oligonucleotides comprising CpG motifs (Krieg Vaccine 2000, 19, 618-622; WO 96/02555, WO 98/16247, WO 98/18810, WO 98/40100, WO 98/55495, WO 98/37919 and WO 98/52581), i.e., oligonucleotides containing at least one CG dinucleotide, where the cytosine is unmethylated; (8) a polyoxyethylene ether or a polyoxyethylene ester e.g. WO 99/52549; (9) a polyoxyethylene sorbitan ester surfactant in combination with an octoxynol (WO 01/21207) or a polyoxyethylene alkyl ether or ester surfactant in combination with at least one additional non-ionic surfactant such as an octoxynol (WO 01/21152); (10) a saponin and an immunostimulatory oligonucleotide (e.g. a CpG oligonucleotide) (WO 00/62800); (11) an immunostimulant and a particle of metal salt e.g. WO 00/23105; (12) a saponin and an oil-in-water emulsion e.g. WO 99/11241; (13) a saponin (e.g. QS21)+3dMPL+IM2 (optionally including a sterol) e.g. WO 98/57659; (14) alphaGalCer and its derivatives; (16) toll-like receptor (TLR) agonists, NOD-like receptor (NLR) agonists, RIG-I agonists, agonists for C-type lectin receptors and other pathogen

recognition receptor (PRR) agonists e.g., CpG ODNs, ISS-ODNs, rinatolimod, polyI:C and its derivatives, flagellin, ampligen, imidazoquinalines (e.g., imiquimod, resiquimod), muramyl dipeptides; (17) other substances that act as immunostimulating agents to enhance the efficacy of the composition. Muramyl peptides include N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-25 acetyl-normuramyl-L-alanyl-D-isoglutamine (nor-MDP), N-acetylmuramyl-L-alanyl-D-isoglutarninyl-L-alanine-2-(1'-2'-dipalmitoyl-sn-glycero-3-hydroxyphosphoryloxy)-ethylamine MTP-PE), etc. Adjuvants suitable for administration to a human included in some cases.

[00130] Further exemplary adjuvants include, but are not limited to: cholera toxin B subunit, BCG, Pseudomonas aeruginosa exoprotein A, tocopherol, HBV core, E. coli heat labile toxins (such as LT-A, LT-B), Pertussis toxin, Diphtheria toxoid, tetanus toxoid, Cholera toxin derived (CTA1-DD, CT), mutant LT and CT, Aluminium salt-based adjuvants (such as Alum, Aluminum phosphate, Aluminum sulphate, Alhydrogel), Calcium phosphate, kaolin, monophosphoryl lipid A (MPL^R) and its derivatives, glucoppyranosyl lipid A, synthetic lipid A, Lipid A mimetics, Vitamin E, Depovax™, Saponins (Quil-A, AS01, AS02 (squalene+MPL+QS-21)), AS03, AS04 (alum+MPL^R), Tomatin, Protolin, RC-529, Pluronic™, Monatides, Matrix-M, OM-174, Lipovac, IC-31, bacterial/mycobacterial peptides (such as KLK, cationic (poly)peptides, anti-bacterial microbial peptides, defensins, tuftsin, cathelicidin), dipeptides (such as pidotimod), Bestatin, Hepon (tetradecapeptide), SCV-07 (gamma-D-glutamyl-L-tryptophan), Thymosin-a, Immunofan, Thymogen, Indolicidin and its derivatives, polyphosphagene and its derivatives, Gellan, nucleotides (mononucleotides, dinucleotides, polynucleotides, cyclic nucleotides), Eurocine etc.

[00131] An immunomodulatory composition of the present disclosure can comprise, in addition to CC, one or more mucoadhesives such as sodium alginate, starch, lectins, thiolated polymers, GelVac™, sodium carboxymethylcellulose, hydroxylpropyl methylcellulose, carbomers, cetyl trimethyl ammonium bromide.

[00132] An immunomodulatory composition of the present disclosure can comprise, in addition to CC, one or more adjuvant formulations such as oil-in-water emulsions, water-in-oil emulsions, nanoemulsions, particulate delivery systems, liposomes, microspheres, biodegradable microspheres, patches virosomes, proteoliposomes, proteasomes, Immunostimulatory complexes (ISCOMs, ISCOMATRIX), microparticles, nanoparticles, biodegradable nanoparticles, silicon nanoparticles, polymeric micro/nano particles, polymeric lamellar substrate particles (PLSP), microparticle resins, nanolipogels,

synthetic/biodegradable and biocompatible semisynthetic or natural polymers or dendrimers (such as PLG, PLGA, PLA, polycaprolactone, silicone polymer, polyesters, poly-dimethyl siloxane, sodium polystyrene sulphonate, polystyrene benzyl trimethyl ammonium chloride, polystyrene divinyl benzene resin, polyphosphazene, poly-[di-(carboxylactophenoxy)phosphazene] (PCPP), poly-(methylmethacrylate), dextran, polyvinylpyrrolidone, hyaluronic acid and derivatives, chitosan and its derivatives, polysaccharides, Delta inulin polysaccharide, glycolipids (synthetic or natural), lipopolysaccharides, polycationic compound(s) (such as Poly-amino acids, poly-(γ-glutamic acid), poly-arginine-HCl, poly-L-lysine, polypeptides, biopolymers), cationic dimethyldioctadecyl ammonium (DDA), alpha-galactosyl ceramide and its derivatives, archaeal lipids and derivatives, lactanes, gallen, glycerolipids, phospholipids, cochleates, etc. or mixtures thereof.

[00133] An immunomodulatory composition of the present disclosure can comprise, in addition to CC, one or more adjuvant formulations such as oil-in-water emulsions or water-in-oil emulsions including edible oils (such as olive oil, mustard oil, vegetable oil, soybean oil, mineral oil etc.).

[00134] An immunomodulatory composition of the present disclosure can comprise, in addition to CC, one or more surfactants and detergents (e.g., non-ionic detergents or niosomes) (such as Tween-80, Polysorbate 80, Span 85, Stearyl tyrosine etc.). An immunomodulatory composition of the present disclosure can comprise, in addition to CC, an component or adjuvant mentioned above which provides a depot effect.

Probiotic

[00135] An immunomodulatory composition of the present disclosure can comprise, in addition to CC, one or more probiotics. "Probiotic" refers to a composition containing one species (i.e., a single isolate) or a combination of pure bacteria (i.e., co-culture of desired bacteria), and may also include any additional carriers, excipients, and/or therapeutic agents that can be administered to a mammal for restoring microbiota and/or providing health benefits. Examples of probiotics include but are not limited to, *Lactobacillus* sp., *Bifidobacteria* sp., *Saccharomyces boulardii*, *Streptococcus* sp., *Enterococcus faecium*, *Bacillus coagulans*, *Faecalibacterium* sp., etc.

Prebiotic

[00136] An immunomodulatory composition of the present disclosure can comprise, in addition to CC, one or more prebiotic. As used herein the term "prebiotic" refers to nutritional supplements that are not digested by the mammal that ingests them, but which

are a substrate for the growth or activity of the microbiota, particularly the gut microbiota. Many prebiotics are carbohydrates, e.g. polysaccharides and oligosaccharides, but the definition does not preclude non-carbohydrates. The most prevalent forms of prebiotics are nutritionally classed as soluble fiber. Prebiotics may provide for changes in the composition and/or activity of the gastrointestinal microbiota. "Prebiotic" also refers to compositions containing non-viable food components that are specifically metabolized in the body by indigenous bacteria thought to be of positive value such as *Bifidobacteria*, *Lactobacillus*, etc. Examples of prebiotics include but are not limited to fructose, xylose, soya, glucose, mannose etc.

Microbiota

[00137] The term "microbiota", "microbiome", "symbiotic" or "commensal" used interchangeably, refers to microbial population (bacteria, viruses, fungi, parasites) in an individual at various places such as gut, skin, saliva, colon, vagina, lungs etc. A dysbalance in microbiota is related to the etiology or onset of several autoimmune and inflammatory diseases. An immunomodulatory composition of the present disclosure can comprise, in addition to CC, members of microbiota of an individual such as *Bacteroidetes*, *Proteobacteria*, *Firmicutes*, *Verrucomicrobia*, *Bacteriodales*, *Enterobacteriales*, *Clostridium*, etc. Other examples of members of microbiota are known, or will be apparent, to those skilled in the art. See, US Patent Application No. 2014/0010844. See, Howarth and Wang, *Nutrients*. 2013, 5(1):58-81 for a description of the role of endogenous microbiota, probiotics and their biological products. Thus a composition of the invention can be used to establish, modulate, regulate or maintain a balanced microbiota. Members of the microbiome can be of autologous, allogeneic and xenogeneic origin, wild-type, viable, inactivated, heat-killed, mutated, attenuated and/or genetically engineered.

Therapeutic pathogens

[00138] An immunomodulatory composition of the present disclosure can comprise, in addition to CC, therapeutic pathogenic bacteria, virus, fungus etc. such as *Listeria*, *Saccharomyces*, *Escherichia*, *Salmonella*, *Staphylococcus*, *Klebsiella*, poxviruses, adenoviruses, oncolytic viruses. Other examples of therapeutic microbial pathogens are known, or will be apparent, to those skilled in the art. See, US Patent Application No. 2014/0010844. Therapeutic pathogen can be wild-type, viable, inactivated, heat-killed, mutated, attenuated and/or genetically engineered.

Therapeutic agents

[00139] An immunomodulatory composition of the present disclosure can comprise, in addition to CC, one or more therapeutic agents. Examples of therapeutic agents are known, or will be apparent, to those skilled in the art. Non-limiting examples of the therapeutic agents are provided herein the "Methods" section, which include anti-inflammatory agents, anti-proliferative agents, immunosuppressive agents, anti-histamines, immunoregulatory agents, immunomodulatory agents, antimetabolic agents, anti-allergic agents, cytotoxic agents, anti-helminth agents, anti-angiogenic agents, antimicrobial agents (such as antiviral agents, antibacterial agents, anti-parasitic agents, antimalarial agents, anti-protozoal agents), therapeutic peptides etc.

METHODS

[00140] The present disclosure provides methods of modulating an immune response in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of the present disclosure. The present disclosure provides methods of reducing an undesired immune response in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of the present disclosure. The present disclosure provides methods of reducing inflammation in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of the present disclosure. The present disclosure provides methods of treating an autoimmune disorder in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of the present disclosure. The present disclosure provides methods of treating an allergy (allergic disease) in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of the present disclosure. The present disclosure provides methods of treating a metabolic disease in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of the present disclosure. The present disclosure provides methods of treating a neurological disorder in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of the present disclosure. The present disclosure provides methods of enhancing the efficacy and/or reducing the toxicity of therapeutic treatment in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of the present disclosure. The present disclosure

provides methods of treating, restoring or correcting disease- or medical condition-related to imbalances in the microbiome of an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of the present disclosure. The present disclosure provides methods of treating, restoring or correcting dysbiosis of an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of the present disclosure.

[00141] The present disclosure also provides a method of modulating dendritic cells, the method comprising: a) contacting dendritic cells (DCs) obtained from an individual with a composition comprising: i) *Caulobacter crescentus*; and/or ii) an antigen; the contacting step is *in vitro*, and modulates antigen presentation of the antigen on the DCs, thereby generating a population of modulated DCs. The population of modulated DCs can then be administered to the individual from whom the DCs were obtained.

[00142] In some cases, various immune cells can be obtained from lymphoid tissues, peripheral blood, organs and tissues, and/or can be differentiated from stem cells obtained from bone marrow or various organs.

[00143] The present disclosure also provides a method of inducing proliferation, differentiation and/or modulation of stem cells, the method comprising contacting stem cells obtained from an individual with a composition comprising *Caulobacter crescentus*. Contacting the stem cells with the CC leads to proliferation, differentiation and/or modulation of the stem cells, thereby generating a population of expanded, differentiated and/or modulated cells. The population of expanded, differentiated and/or modulated cells can then be administered to the individual from whom the stem cells were obtained.

[00144] The present disclosure further provides a method of generating regulatory lymphocytes such as NK, NKT, γδ T cells, ILCs, T cells, and B cells, the method comprising: a) contacting lymphocytes (NK, NKT, γδ T cells, ILCs, T cells, B cells) obtained from an individual with a composition comprising: i) *Caulobacter crescentus*; and/or ii) an antigen in the presence or absence of antigen presenting cells. Contacting the lymphocytes with the CC generates regulatory lymphocytes, thereby generating a population of regulatory lymphocytes. The population of regulatory lymphocytes can then be administered to the individual from whom the lymphocytes were obtained.

Methods of modulating an immune response

[00145] The present disclosure provides methods of modulating an immune response in an individual, the method comprising administering to the individual an effective amount

of an immunomodulatory composition of the present disclosure. The present disclosure provides methods of reducing an undesired immune response in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of the present disclosure. The present disclosure provides methods of reducing inflammation in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of the present disclosure. The present disclosure provides methods of treating an autoimmune disorder in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of the present disclosure. The present disclosure provides methods of treating an allergy (allergic disease) in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of the present disclosure.

[00146] In some cases, the immune response is a humoral immune response. In some cases, the present disclosure provides methods of modulating a humoral immune response in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of the present disclosure. In some cases, the immunomodulatory composition does not include any additional antigens (other than antigens present on CC). In some cases, the immunomodulatory composition comprises an antigen (e.g., an antigen other than antigens present on CC). As described above, suitable antigens include autoantigens, and allergens.

[00147] In some cases, the immune response is a cellular immune response. In some cases, the present disclosure provides methods of modulating a cellular immune response in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of the present disclosure. In some cases, the immunomodulatory composition does not include any additional antigens (other than antigens present on CC). In some cases, the immunomodulatory composition comprises an antigen (e.g., an antigen other than antigens present on CC). As described above, suitable antigens include autoantigens and allergens.

[00148] In some cases, the immune response comprises a modulation in the number of B cells. In some cases, a subject method comprising administering to an individual in need thereof an effective amount of an immunomodulatory composition, where an effective amount of an immunomodulatory composition is an amount that, when administered to the individual in a single dose or in multiple doses, is effective to modulate (e.g., reduce) the number of B cells in an individual. For example, in some cases, an effective amount

of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number of B cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, or more than 10-fold, compared to the number of B cells in the individual in the absence of treatment with the immunomodulatory composition. In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number of antigen-specific B cells in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number of antigen-specific B cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, or more than 10-fold, compared to the number of antigen-specific B cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the number of antigen-specific B cells in an individual by 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 75%, or more than 75%, compared to the number of antigen-specific B cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the number of autoantigen-specific B cells in an individual by 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 75%, or more than 75%, compared to the number of autoantigen-specific B cells in the individual in the absence of treatment with the immunomodulatory composition.

[00149] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) activation of B cells in an individual. For

example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) activation of B cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the activation level of B cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the activation of B cells in an individual by 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 75%, or more than 75%, compared to the activation level of B cells in the individual in the absence of treatment with the immunomodulatory composition.

[00150] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the amount of antibody specific to a given antigen in the individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the amount of antibody specific to a given antigen in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, or more than 10-fold, compared to the amount of antibody specific to the antigen in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the amount of antibody specific to a given antigen in an individual by 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 75%, or more than 75%, compared to the amount of antibody specific to the antigen in the individual in the absence of treatment with the immunomodulatory composition.

[00151] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in

multiple doses, to modulate (e.g., reduce) production of one or more cytokines in the individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) production of one or more cytokines in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, or more than 10-fold, compared to the amount of the cytokine in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the production of one or more cytokines in an individual by 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 75%, or more than 75%, compared to the production of one or more cytokines in the individual in the absence of treatment with the immunomodulatory composition. In other cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) production of GM-CSF in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, or more than 10-fold, compared to the amount of GM-CSF in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the production of GM-CSF in an individual by 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 75%, or more than 75%, compared to the amount of GM-CSF in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) production of IL-22 in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, or more

than 10-fold, compared to the amount of IL-22 in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the production of IL-22 in an individual by 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 75%, or more than 75%, compared to the amount of IL-22 in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) production of interferon (IFN)-α and/or IFN-β and/or IFN-γ in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, or more than 10-fold, compared to the amount of IFN-α or IFN-β or IFN-γ in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the production of interferon (IFN)-α and/or IFN-β and/or IFN-γ in an individual by 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 75%, or more than 75%, compared to the amount of interferon (IFN)-α and/or IFN-β and/or IFN-γ in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) production of one or more of IL-17A, IL-2, IL-10, IL-6 and/or TNF-α in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, or more than 10-fold, compared to the amount of IL-17A, IL-2, IL-10, IL-6, or TNF-α in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the production of one or more of IL-17A, IL-2, IL-10, IL-6 and

TNF-αin an individual by 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 75%, or more than 75%, compared to the amount of IL-17A, IL-2, IL-10, IL-6 and TNF-α in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the production of IL-6 in an individual by 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 75%, or more than 75%, compared to the amount of IL-6 in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the production of IL-1β in an individual by 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 75%, or more than 75%, compared to the amount of IL-1β in the individual in the absence of treatment with the immunomodulatory composition. In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to increase the level of TGF-β in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, or more than 10-fold, compared to the amount of TGF-β in the individual in the absence of treatment with the immunomodulatory composition.

[00152] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., increase, reduce or balance) production of one or more cytokines, chemokines or lymphotoxins such as but not limited to GM-CSF, IL-2, IL-22, Interferons, IL-1β, TGF-β, IL-17A, IL-2, IL-10, IL-6, IL-5, IL-13, TNF-α, IL-9, IL-28 KC/IL-8, MIP-1α, LTα4, etc. in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, or more than 10-fold, compared to the amount of cytokines, chemokines or lymphotoxins such as but not limited to GM-CSF, IL-2, IL-22, Interferons, IL-1β, TGF-β, IL-17A, IL-2, IL-10,

IL-6, IL-5, IL-13, TNF-α, IL-9, IL-28, KC/IL-8, MIP-1α, LTα4, etc., in the individual in the absence of treatment with the immunomodulatory composition.

[00153] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) a Th1 response in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) a Th1 response in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the level of the Th1 response in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the Th1 response in an individual by 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 75%, or more than 75%, compared to the Th1 response in the individual in the absence of treatment with the immunomodulatory composition.

[00154] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of $CD4^+$ T cells in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of $CD4^+$ T cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number and/or activity of $CD4^+$ T cells in the individual in the absence of treatment with the immunomodulatory composition. In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to

modulate (e.g., reduce) the number and/or activity of antigen-specific $CD4^+$ T cells in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of antigen-specific $CD4^+$ T cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number and/or activity of antigen-specific $CD4^+$ T cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the number and/or activity of $CD4^+$ T cells in an individual by 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 75%, or more than 75%, compared to the number and/or activity of $CD4^+$ T cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the number and/or activity of antigen-specific $CD4^+$ T cells in an individual by 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 75%, or more than 75%, compared to the number and/or activity of antigen-specific $CD4^+$ T cells in the individual in the absence of treatment with the immunomodulatory composition.

[00155] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of $CD8^+$ T cells in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of $CD8^+$ T cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more

than 100-fold, compared to the number and/or activity of $CD8^+$ T cells in the individual in the absence of treatment with the immunomodulatory composition. In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of antigen-specific $CD8^+$ T cells in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of antigen-specific $CD8^+$ T cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number and/or activity of antigen-specific $CD8^+$ T cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the number and/or activity of $CD8^+$ T in an individual by 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 75%, or more than 75%, compared to the number and/or activity of $CD8^+$ T in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the number and/or activity of antigen-specific $CD8^+$ T in an individual by 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 75%, or more than 75%, compared to the number and/or activity of antigen-specific $CD8^+$ T in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the number and/or activity of autoantigen-specific $CD8^+$ T cells in an individual by 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 75%, or more than 75%, compared to the

number and/or activity of autoantigen-specific $CD8^+$ T cells in the individual in the absence of treatment with the immunomodulatory composition.

[00156] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of cytolytic T cells in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of cytolytic T cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number and/or activity of cytolytic T cells in the individual in the absence of treatment with the immunomodulatory composition. In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of antigen-specific cytolytic T cells in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of antigen-specific cytolytic T cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number and/or activity of antigen-specific cytolytic T cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the number and/or activity of cytolytic T cells in an individual by 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 75%, or more than 75%, compared to the number and/or activity of cytolytic T cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an

effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the number and/or activity of antigen-specific cytolytic T cells in an individual by 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 75%, or more than 75%, compared to the number and/or activity of antigen-specific cytolytic T cells in the individual in the absence of treatment with the immunomodulatory composition.

[00157] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate the number and/or activity of one or more of natural killer (NK) cells, NKT cells, γδ T cells, ILCs, macrophages, and dendritic cells (DCs) in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate the number and/or activity of one or more of NK cells, NKT cells, γδ T cells, ILCs, macrophages,and DCs in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number and/or activity of one or more of NK cells, NKT cells, γδ T cells, ILCs, macrophages, and DCs in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate the number and/or activity of one or more of NK cells, NKT cells, γδ T cells, ILCs, macrophages, and DCs in an individual by 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 75%, or more than 75%, compared to the number and/or activity of NK cells, NKT cells, γδ T cells, ILCs, macrophages, and DCs in the individual in the absence of treatment with the immunomodulatory composition.

[00158] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to increase, decrease or balance the number and/or function of regulatory cells in an individual. Tregs (regulatory T cells) are $CD4^+$ or $CD8^+$, and may also be

$FoxP3^+$. Tregs may also be defined by other markers such as PD-1, CTLA-4 etc. Regulatory cells may also be comprised of other innate cells such as NK, NKT, γδ T cells, ILCs, and DCs, and B lymphocytes. NK and NKT can also be $FoxP3^+$ and may also be defined by other markers such as PD-1. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate the number of regulatory cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared number and/or activity of regulatory cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to increase the number of regulatory cells in an individual by 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 75%, or more than 75%, compared to the number of regulatory cells in the individual in the absence of treatment with the immunomodulatory composition.

[00159] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of Th17 cells in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of Th17 cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number and/or activity of Th17 cells in the individual in the absence of treatment with the immunomodulatory composition. In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of antigen-specific Th17 cells in an

individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of antigen-specific Th17 cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number and/or activity of antigen-specific Th17 cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the number and/or activity of Th17 cells in an individual by 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 75%, or more than 75%, compared to the number and/or activity of Th17 cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the number and/or activity of antigen-specific Th17 cells in an individual by 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 75%, or more than 75%, compared to the number and/or activity of antigen-specific Th17 cells in the individual in the absence of treatment with the immunomodulatory composition.

[00160] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of Th22 cells in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of Th22 cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number and/or activity of Th22 cells in the individual in

the absence of treatment with the immunomodulatory composition. In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of antigen-specific Th22 cells in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of antigen-specific Th22 cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number and/or activity of antigen-specific Th22 cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the the number and/or activity of Th22 cells in an individual by 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 75%, or more than 75%, compared to the the number and/or activity of Th22 cells in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the the number and/or activity of antigen-specific Th22 cells in an individual by 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 75%, or more than 75%, compared to the the number and/or activity of antigen-specificTh22 cells in the individual in the absence of treatment with the immunomodulatory composition.

[00161] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate the number and/or activity of TH9 cells in an individual. "Modulate the number and/or activity" of TH9 cells, as used herein, refers to increasing, decreasing, or balancing the number and/or activity of TH9 cells. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in

multiple doses, to modulate the number and/or activity of TH9 cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared number and/or activity of TH9 cells in the individual in the absence of treatment with the immunomodulatory composition.

[00162] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) innate and/or adaptive (including both cellular and humoral) immune responses in an individual. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the number and/or activity of innate and/or adaptive immune cells and/or their effector functions in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number and/or activity of one or more of innate or adaptive immune cells and/or their effector functions in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the the number and/or activity of innate and/or adaptive immune cells and/or their effector functions in an individual by 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 75%, or more than 75%, compared to the the number and/or activity of innate and/or adaptive immune cells and/or their effector functions in the individual in the absence of treatment with the immunomodulatory composition.

[00163] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to induce and/or augment apoptosis in innate and/or adaptive immune cells in an individual to protect from undesirable inflammation. For example, in some cases, an effective amount of an immunomodulatory composition of the present

disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to induce and/or augment apoptosis in innate and/or adaptive immune cells in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the number of one or more of innate or adaptive immune cells in the individual in the absence of treatment with the immunomodulatory composition.

[00164] In some cases, an immunomodulatory composition of the present disclosure comprises CC and an antigen. Where an immunomodulatory composition of the present disclosure comprises CC and an antigen, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) an immune response to the antigen by at least about 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the immune response to the antigen in the absence of treatment with the immunomodulatory composition. For example, where the antigen is an antigen associated with or derived from an autoantigen or an allergen, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) an immune response to the antigen by at least about 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the immune response to the antigen in the absence of treatment with the immunomodulatory composition. For example, where the immunomodulatory composition comprises CC, an antigen, an autoantigen or an allergen, alone or in combination with each other, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the immune response to the antigen in an individual by 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

75%, or more than 75%, compared to the immune response to the antigen in the individual in the absence of treatment with the immunomodulatory composition.

[00165] The immune response can be a humoral immune response, e.g., a B cell or antibody immune response. Thus, e.g., in some cases, where the antigen is an antigen associated with or derived an autoantigen or an allergen, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) a B cell response to the antigen by at least about 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the B cell response to the antigen in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the B cell response to the antigen in an individual by 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 75%, or more than 75%, compared to the B cell response to the antigen in the individual in the absence of treatment with the immunomodulatory composition. For example, in some cases, where the antigen is an antigen associated with or derived from an autoantigen or an allergen, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) the amount of antibody specific to the antigen by at least about 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the amount of antibody specific to the antigen in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the amount of antibody specific to the antigen in an individual by 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 75%, or more than 75%, compared to the amount of antibody specific to the

antigen in the individual in the absence of treatment with the immunomodulatory composition.

[00166] The immune response can be a cellular immune response, e.g., a T cell immune response. Thus, e.g., in some cases, where the antigen is an antigen associated with or derived from an autoantigen or an allergen, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to modulate (e.g., reduce) a T cell response to the antigen by at least about 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the T cell response to the antigen in the absence of treatment with the immunomodulatory composition. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to reduce the T cell response to the antigen in an individual by 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 75%, or more than 75%, compared to the T cell response to the antigen in the individual in the absence of treatment with the immunomodulatory composition. In some cases, the immune response is a humoral immune response and a cellular immune response.

[00167] In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to normalize the level of one or more serum markers of pathological immune responses. For example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, in normalizing the level of one or more of the serum markers (these markers include, but are not restricted to, cholesterol (CHOL), glucose (GLU), globulin (GLOB), alanine aminotransferases (ALT), aspartate aminotransferases (AST), total phosphates (TP), total bilirubin (TBIL), phosphate (PHOS), triglycerides (TRIG), uric acid (URIC), creatine kinase (CK) and urea) in an individual by 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 75%, or more than 75%, compared with the level of CHOL, GLU, GLOB, ALT, AST, TP, PHOS, TRIG, URIC, CK, TBIL

or urea in the individual in the absence of treatment with the immunomodulatory composition.

Adjuvants

[00168] In some embodiments, a subject method involves administration of a subject immunomodulatory composition, where the immunomodulatory composition comprises CC and one or more adjuvants.

[00169] Exemplary adjuvants include, but are not limited to: (1) oil-in-water emulsion formulations (with or without other specific immunostimulating agents such as muramyl peptides (see below) or bacterial cell wall components), such as for example (a) MF59™ (WO 90/14837; Chapter 10 in Vaccine design: the subunit and adjuvant approach, eds. Powell & Newman, Plenum Press 1995), containing 5% Squalene, 0.5% Tween 80, and 0.5% Span 85 (optionally containing MTP-PE) formulated into submicron particles using a microfluidizer, (b) SAF, containing 10% Squalane, 0.4% Tween 80, 5% pluronic-blocked polymer L121, and thr-MDP either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion, and (c) RIBI™ adjuvant system (RAS), (Ribi Immunochem, Hamilton, Mont.) containing 2% Squalene, 0.2% Tween 80, and one or more bacterial cell wall components such as monophosphorylipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), e.g., MPL+CWS (Detox™); (2) saponin adjuvants, such as QS21 or Stimulon™(Cambridge Bioscience, Worcester, Mass.) may be used or particles generated therefrom such as ISCOMs (immunostimulating complexes), which ISCOMS may be devoid of additional detergent e.g. WO 00/07621; (3) Complete Freund's Adjuvant (CFA) and Incomplete Freund's Adjuvant (IFA); (4) cytokines, such as interleukins (e.g. IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12, IL-15, IL-28, etc.) (WO99/44636), etc.), interferons (e.g. gamma interferon), macrophage colony stimulating factor (M-CSF), tumor necrosis factor (TNF), colony-stimulating factors (e.g., GM-CSF), etc.; (5) monophosphoryl lipid A (MPL) or 3-O-deacylated MPL (3dMPL) e.g. GB-2220221, EP-A-0689454, optionally in the substantial absence of alum when used with pneumococcal saccharides e.g. WO 00/56358; (6) combinations of 3dMPL with, for example, QS21 and/or oil-in-water emulsions e.g. EP-A-0835318, EP-A-0735898, EP-A-0761231; (7) oligonucleotides comprising CpG motifs (Krieg Vaccine 2000, 19, 618-622; WO 96/02555, WO 98/16247, WO 98/18810, WO 98/40100, WO 98/55495, WO 98/37919 and WO 98/52581), i.e., oligonucleotides containing at least one CG dinucleotide, where the cytosine is unmethylated; (8) a polyoxyethylene ether or a polyoxyethylene ester e.g. WO 99/52549; (9) a

polyoxyethylene sorbitan ester surfactant in combination with an octoxynol (WO 01/21207) or a polyoxyethylene alkyl ether or ester surfactant in combination with at least one non-ionic surfactant such as an octoxynol (WO 01/21152); (10) a saponin and an immunostimulatory oligonucleotide (e.g. a CpG oligonucleotide) (WO 00/62800); (11) an immunostimulant and a particle of metal salt e.g. WO 00/23105; (12) a saponin and an oil-in-water emulsion e.g. WO 99/11241; (13) a saponin (e.g. QS21)+3dMPL+IM2 (optionally including a sterol) e.g. WO 98/57659; (14) alphaGalCer and its derivatives; (16) toll-like receptor (TLR) agonists, NOD-like receptor (NLR) agonists, RIG-I agonists, agonists for C-type lectin receptors and other pathogen recognition receptor (PRR) agonists e.g., CpG ODNs, ISS-ODNs, rinatolimod, polyI:C and its derivatives, flagellin, ampligen, imidazoquinalines (e.g., imiquimod, resiquimod), muramyl dipeptides; (17) other substances that act as immunostimulating agents to enhance the efficacy of the composition. Muramyl peptides include N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-25 acetyl-normuramyl-L-alanyl-D-isoglutamine (nor-MDP), N-acetylmuramyl-L-alanyl-D-isoglutarninyl-L-alanine-2-(1'-2'-dipalmitoyl-sn-glycero-3-hydroxyphosphoryloxy)-ethylamine MTP-PE), etc. Adjuvants suitable for administration to a human included in some cases.

[00170] Further exemplary adjuvants include, but are not limited to: cholera toxin B subunit, BCG, Pseudomonas aeruginosa exoprotein A, tocopherol, HBV core, E. coli heat labile toxins (such as LT-A, LT-B), Pertussis toxin, Diphtheria toxoid, tetanus toxoid, Cholera toxin derived (CTA1-DD, CT), mutant LT and CT, Aluminium salt-based adjuvants (such as Alum, Aluminum phosphate, Aluminum sulphate, Alhydrogel), Calcium phosphate, kaolin, monophosphoryl lipid A (MPL^R) and its derivatives, glucoppyranosyl lipid A, synthetic lipid A, Lipid A mimetics, Vitamin E, Depovax™, Saponins (Quil-A, AS01, AS02 (squalene+MPL+QS-21)), AS03, AS04 (alum+MPL^R), Tomatin, Protolin, RC-529, Pluronic™, Monatides, Matrix-M, OM-174, Lipovac, IC-31, bacterial/mycobacterial peptides (such as KLK, cationic (poly)peptides, anti-bacterial microbial peptides, defensins, tuftsin, cathelicidin), dipeptides (such as pidotimod), Bestatin, Hepon (tetradecapeptide), SCV-07 (gamma-D-glutamyl-L-tryptophan), Thymosin-a, Immunofan, Thymogen, Indolicidin and its derivatives, polyphosphagene and its derivatives, Gellan, nucleotides (mononucleotides, dinucleotides, polynucleotides, cyclic nucleotides), Eurocine etc.

Combination therapy

[00171] In some embodiments, a subject method involves administration of a subject immunomodulatory composition as monotherapy, e.g., administration of a subject immunomodulatory composition only, without co-administration of any other therapeutic agent. In other embodiments, a subject treatment method is a combination therapy involving administration of: a) a subject immunomodulatory composition; and b) at least one additional therapeutic agent (or a pharmaceutically acceptable salt, prodrugs, salts of prodrugs, stereoisomers, tautomers etc. of the therapeutic agent), where the immunomodulatory composition and the at least one additional therapeutic agent are administered in combined amounts that are effective to modulate an immune response. Suitable additional therapeutic agents are described below.

[00172] A subject combination therapy can involve: a) administration of an immunomodulatory composition and at least one additional therapeutic agent at the same time, in the same formulation or in separate formulations; b) administration of at least one additional therapeutic agent within about 5 minutes to about 4 weeks of administration of an immunomodulatory composition, e.g., administration of at least one additional therapeutic agent within about 5 minutes to about 15 minutes, within about 15 minutes to about 30 minutes, within about 30 minutes to about 60 minutes, within about 1 hour to about 2 hours, within about 2 hours to about 4 hours, within about 4 hours to about 8 hours, within about 8 hours to about 12 hours, within about 12 hours to about 24 hours, within about 24 hours to about 2 days, within about 2 days to about 4 days, within about 4 days to about 7 days, within about 1 week to about 2 weeks, or within about 2 weeks to about 4 weeks of administration of an immunomodulatory composition.

[00173] In some embodiments, the at least one additional therapeutic agent is co-formulated with the immunomodulatory composition. In other embodiments, the at least one additional therapeutic agent and the immunomodulatory composition are separately formulated.

[00174] In some embodiments, an effective amount of an immunomodulatory composition and an at least one additional therapeutic agent are synergistic amounts. As used herein, a "synergistic combination" or a "synergistic amount" of a subject immunomodulatory composition and an additional (e.g., a second) therapeutic agent is a combination or amount that is more effective in the therapeutic or prophylactic treatment of a disease than the incremental improvement in treatment outcome that could be predicted or expected from a merely additive combination of (i) the therapeutic or

prophylactic benefit of the immunomodulatory composition when administered at that same dosage as a monotherapy and (ii) the therapeutic or prophylactic benefit of the additional therapeutic agent when administered at the same dosage as a monotherapy.

[00175] A subject combination therapy can involve: administration of an immunomodulatory composition and at least one additional form of therapy such as radiation therapy (comprising radioisotopes such as ^{125}I, strontium-89, ^{32}P, alpha-emitting isotopes, beta-emitting isotopes etc.), photodynamic therapy, laser therapy, natural product therapy, nutraceutical therapy, cellular therapy, prebiotic therapy, probiotic therapy, symbiotic therapy, paraprobiotic therapy etc., given at the same or different times.

[00176] A subject combination therapy can involve: administration of an immunomodulatory composition and at least one additional form of therapy such as one or more members of microbiota of an individual such as *Bacteroidetes*, *Proteobacteria*, *Firmicutes*, *Verrucomicrobia*, *Bacteriodales*, *Enterobacteriales*, *Clostridium* , VSL#3 etc. given at the same or different times. Thus, the present invention can be used to establish, modulate, regulate or maintain a balanced microbiota. Members of the microbiome can be wild-type, viable, inactivated, heat-killed, mutated, attenuated and/or genetically engineered.

[00177] A subject combination therapy can involve: administration of an immunomodulatory composition and at least one additional form of therapy such as one or more members of probiotics.

[00178] A subject combination therapy can involve: administration of an immunomodulatory composition and at least one additional form of therapy such as one or more members of therapeutic pathogenic bacteria, virus, fungus etc. such as *Listeria*, *Saccharomyces*, *Escherichia*, *Salmonella*, *Staphylococcus*, *Klebsiella*, poxviruses, adenoviruses, oncolytic viruses. Therapeutic pathogen can be wild-type, mutated, attenuated and/or genetically engineered. Members of the therapeutic pathogens can be wild-type, viable, inactivated, heat-killed, mutated, attenuated and/or genetically engineered.

[00179] In some embodiments, an effective amount of an immunomodulatory composition can be administered in a heterologous or homologous prime-boost vaccine, immunotherapy and/or chemotherapy regimen(s).

[00180] A subject combination therapy can involve: administration of an immunomodulatory composition and a therapeutic vaccine.

[00181] A subject combination therapy can involve: administration of an immunomodulatory composition and a therapeutic antibody. For example, in some embodiments, a subject method involves: a) administration of an immunomodulatory composition of the present disclosure; and b) administration of at least one antibody. The CC and the antibody can be in the same formulation or in separate formulations. The CC and the antibody can be administered simultaneously, or at different times. Suitable antibodies include an antibody against a cancer antigen or a pathogenic antigen (e.g., a therapeutic antibody, monoclonal antibodies, bispecific antibodies, chemoimmuno conjugated antibodies, radioimmunoconjugated antibodies, antibody-cytokine fusion proteins, antibody-antigen fusion proteins, antibody-immunotoxin fusion protein etc.). Suitable antibodies include, without limitation, antibodies directed against co-stimulatory or co-inhibitory molecules (CD28, CD40, ICOS, CD137, OX40, CD137, CD227, CTLA-4, PD-1, KIRs, TCR, PDL1, LAG3, TIM3, VISTA etc.); and other therapeutic antibodies. Non-limiting examples of suitable antibodies include, but are not limited to, adalimumab, bevacizumab, infliximab, abciximab, alemtuzumab, bapineuzumab, basiliximab, belimumab, briakinumab, brodalumab, canakinumab, certolizumab pegol, cetuximab, conatumumab, denosumab, eculizumab, etrolizumab, gemtuzumab ozogamicin, golimumab, ibritumomab tiuxetan, labetuzumab, mapatumumab, matuzumab, mepolizumab, motavizumab, muromonab-CD3, natalizumab, nimotuzumab, ofatumumab, omalizumab, oregovomab, palivizumab, panitumumab, pemtumornab, pertuzumab, ranibizumab, rituximab, rovelizumab, tocilizumab, tositumomab, trastuzumab, ustekinumab, vedolizomab, zalutumumab, and zanolimumab.

[00182] Non-limiting examples of therapeutic and prophylactic antibodies that can be used in combination therapy with an immunomodulatory composition of the present disclosure include MDX-010 (Medarex, N.J.) which is a humanized anti-CTLA-4 antibody for the treatment of prostate cancer; SYNAGIS™ (MedImmune, Md.) which is a humanized anti-respiratory syncytial virus (RSV) monoclonal antibody for the treatment of RSV infection; and HERCEPTIN™ (Trastuzumab) (Genentech, Calif.) which is a humanized anti-HER2 monoclonal antibody for the treatment of metastatic breast cancer. Other examples are humanized anti-CD18 $F(ab')_2$ (Genentech); CDP860 which is a humanized anti-CD18 $F(ab')_2$ (Celltech, UK); PRO542 which is an anti-HIV gp120 antibody fused with CD4 (Progenics/Genzyme Transgenics); Ostavir which is a human anti-Hepatitis B virus antibody (Protein Design Lab/Novartis); PROTOVIR™ which is a humanized anti-CMV IgGI antibody (Protein Design Lab/Novartis); MAK-

195 (SEGARD) which is a murine anti-TNF-α $F(ab')_2$ (Knoll Pharma/BASF); IC14 which is an anti-CD14 antibody (ICOS Pharm); a humanized anti-VEGF IgG1 antibody (Genentech); OVAREX™ which is a murine anti-CA 125 antibody (Altarex); PANOREX™ which is a murine anti-17-IA cell surface antigen IgG2a antibody (Glaxo Wellcome/Centocor); BEC2 which is a murine anti-idiotype (GD3 epitope) IgG antibody (ImClone System); IMC-C225 which is a chimeric anti-EGFR IgG antibody (ImClone System); VITAXIN™ which is a humanized anti-αVβ3 integrin antibody (Applied Molecular Evolution/MedImmune); Campath 1H/LDP-03 which is a humanized anti-CD52 IgG1 antibody (Leukosite); Smart M195 which is a humanized anti-CD33 IgG antibody (Protein Design Lab/Kanebo); RITUXAN™ which is a chimeric anti-CD20 IgG1 antibody (IDEC Pharm/Genentech, Roche/Zettyaku); LYMPHOCIDE™ which is a humanized anti-CD22 IgG antibody (Immunomedics); Smart ID10 which is a humanized anti-HLA antibody (Protein Design Lab); ONCOLYM™ (Lym-1) is a radiolabelled murine anti-HLA DIAGNOSTIC REAGENT antibody (Techniclone); ABX-IL8 is a human anti-IL8 antibody (Abgenix); anti-CD11a is a humanized IgG1 antibody (Genentech/Xoma); ICM3 is a humanized anti-ICAM3 antibody (ICOS Pharm); IDEC-114 is a primatized anti-CD80 antibody (IDEC Pharm/Mitsubishi); ZEVALIN™ is a radiolabelled murine anti-CD20 antibody (IDEC/Schering AG); IDEC-131 is a humanized anti-CD40L antibody (IDEC/Eisai); IDEC-151 is a primatized anti-CD4 antibody (IDEC); IDEC-152 is a primatized anti-CD23 antibody (IDEC/Seikagaku); SMART anti-CD3 is a humanized anti-CD3 IgG (Protein Design Lab); 5G1.1 is a humanized anti-complement factor 5 (C5) antibody (Alexion Pharm); D2E7 is a humanized anti-TNF-α antibody (CAT/BASF); CDP870 is a humanized anti-TNF-α Fab fragment (Celltech); IDEC-151 is a primatized anti-CD4 IgG1 antibody (IDEC Pharm/SmithKline Beecham); MDX-CD4 is a human anti-CD4 IgG antibody (Medarex/Eisai/Genmab); CDP571 is a humanized anti-TNF-α IgG4 antibody (Celltech); LDP-02 is a humanized anti-α4β7 antibody (LeukoSite/Genentech); OrthoClone OKT4A is a humanized anti-CD4 IgG antibody (Ortho Biotech); ANTOVA™ is a humanized anti-CD40L IgG antibody (Biogen); ANTEGREN™ is a humanized anti-VLA-4 IgG antibody (Elan); MDX-33 is a human anti-CD64 (FcγR) antibody (Medarex/Centeon); SCH55700 is a humanized anti-IL-5 IgG4 antibody (Celltech/Schering); SB-240563 and SB-240683 are humanized anti-IL-5 and IL-4 antibodies, respectively, (SmithKline Beecham); rhuMab-E25 is a humanized anti-IgE IgG1 antibody (Genentech/Norvartis/Tanox Biosystems); ABX-CBL is a murine anti CD-147 IgM

antibody (Abgenix); BTI-322 is a rat anti-CD2 IgG antibody (MedImmune/Bio Transplant); Orthoclone/OKT3 is a murine anti-CD3 IgG2a antibody (ortho Biotech); SIMULECT™ is a chimeric anti-CD25 IgG1 antibody (Novartis Pharm); LDP-01 is a humanized anti-β_2-integrin IgG antibody (LeukoSite); Anti-LFA-1 is a murine anti CD18 F(ab').sub.2 (Pasteur-Merieux/Immunotech); CAT-152 is a human anti-TGF-β_2 antibody (Cambridge Ab Tech); and Corsevin M is a chimeric anti-Factor VII antibody (Centocor). The above-listed immunoreactive reagents, as well as any other immunoreactive reagents, may be administered according to any regimen known to those of skill in the art, including the regimens recommended by the suppliers of the immunoreactive reagents.

[00183] Other examples of therapeutic and prophylactic antibodies that can be used in combination with an immunomodulatory composition of the present disclosure include Humira and Remicade; ACTEMRA™ (Genentech) which is a recombinant monoclonal IgG1 anti-human interleukin 6-receptor antibody for the treatment of anti-TNF resistant RA and juvenile idiopathic arthritis (JIA); ARZERRA™ (GlaxoSmithKline/Novartis) which is a chimeric human monoclonal antibody directed against membrane proximal epitope on the CD20 molecule for the treatment of RA; BENLYSTA™ (GlaxoSmithKline) which is a human monoclonal IgG1 gamma that binds to and inhibits the soluble form of the B-lymphocyte stimulator (BLyS) protein for the treatment of SLE; ORENCIA™ (Bristol-Myers Squibb) which is a CTLA-4 IgG1 binding to CD80/86 on antigen-presenting cells inhibiting the co-stimulation of CD28 on the T cells for the treatment of RA, JIA and SLE; SIMPONI (Janssen) which is a IgG1 monoclonal antibody acting on both soluble and membrane-bound TNF-α for the treatment of RA, psoriatic arthritis (PsA) and ankylosing spondylitis (AS); CIMZIA™ (UCB Group) which is a pegylated humanized antibody Fab' fragment of the TNF-α monoclonal antibody for the treatment of RA; Sifalimumab (MedImmune) which is an anti-IFN-α monoclonal antibody designed for the treatment of SLE, dematomyositis and polymyositis; various intravenous immunoglobulin products which are pools of immunoglobulins from healthy individuals for the treatment of SLE, systemic sclerosis and vasculitis; KINERET™ (Swedish Oprhan Biovitrum AB), ILARIS™ (Novartis) and ARCALYST™ (Regeneron) which are interleukin-1 blockers for the treatment of RA and cryopyrin-associated periodic syndrome (CAPS).

[00184] A subject combination therapy can involve: administration of an immunomodulatory composition of the present disclosure and one or more cytokines. For

example, in some embodiments, a subject method involves: a) administration of an immunomodulatory composition of the present disclosure; and b) administration of one or more cytokines. The CC and the one or more cytokines can be in the same formulation or in separate formulations. The CC and the one or more cytokines can be administered simultaneously, or at different times. Suitable cytokines include, without limitation, interleukins, transforming growth factors (TGFs), fibroblast growth factors (FGFs), platelet derived growth factors (PDGFs), epidermal growth factors (EGFs), colony stimulating factors (CSFs), connective tissue activated peptides (CTAPs), osteogenic factors, and biologically active analogs, fragments, and derivatives of such growth factors. Suitable cytokines include B/T-cell differentiation factors, B/T-cell growth factors, mitogenic cytokines, chemotactic cytokines, colony stimulating factors, angiogenesis factors, IFN-α, IFN-β, IFN-γ, IL1, IL2, IL3, IL4, IL5, IL6, IL7, IL8, IL9, IL10, IL11, IL12, IL13, IL14, IL15, IL16, IL17, IL18, IL22, etc., leptin, myostatin, macrophage stimulating protein, platelet-derived growth factor, tumor necrosis factor (TNF)-alpha (TNF-α), TNF-β, nerve growth factor (NGF), CD40L, CD137L/4-1BBL, human lymphotoxin-β, G-CSF, M-CSF, GM-CSF, platelet-derived growth factor (PDGF), IL-1α, IL1-β, IP-10, PF4, GRO, 9E3, erythropoietin, endostatin, angiostatin, vascular endothelial growth factor (VEGF) or any fragments or combinations thereof. Other cytokines include members of the transforming growth factor (TGF) supergene family include the beta transforming growth factors (for example TGF-β1, TGF-β2, TGF-β3); bone morphogenetic proteins (for example, BMP-1, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, BMP-9); heparin-binding growth factors (for example, fibroblast growth factor (FGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF)); hematopoietic growth factors (Flt3); pituitary growth hormones or derivatives; growth hormones, neuroactive hormones, Inhibins (for example, Inhibin A, Inhibin B); differentiation factors (for example, GDF-1); and Activins (for example, Activin A, Activin B, Activin AB).

[00185] A subject combination therapy can involve: administration of an immunomodulatory composition of the present disclosure and one or more therapeutic agents such as anti-angiogenic agents (e.g., in methods for the treatment of solid tumors and for the treatment and prevention of metastases) and anti-hormonal agents (particularly in methods for the treatment of hormone-dependent cancers such as breast cancer and prostate cancer).

[00186] In one embodiment, an immunomodulatory composition of the present disclosure is administered in combination with one or more anti-angiogenic agents. Such agents include, without limitation, angiostatin, thalidomide, kringle 5, endostatin, Serpin (Serine Protease Inhibitor) anti-thrombin, 29 kDa N-terminal and a 40 kDa C-terminal proteolytic fragments of fibronectin, 16 kDa proteolytic fragment of prolactin, 7.8 kDa proteolytic fragment of platelet factor-4, a 13-amino acid peptide corresponding to a fragment of platelet factor-4 (Maione et al., 1990, Cancer Res. 51:2077-2083), a 14-amino acid peptide corresponding to a fragment of collagen I (Tolma et al., 1993, J. Cell Biol. 122:497-511), a 19 amino acid peptide corresponding to a fragment of Thrombospondin I (Tolsma et al., 1993, J. Cell Biol. 122:497-511), a 20-amino acid peptide corresponding to a fragment of SPARC (Sage et al., 1995, J. Cell. Biochem. 57:1329-1334), or any fragments, family members, or variants thereof, including pharmaceutically acceptable salts thereof.

[00187] Other peptides that inhibit angiogenesis and correspond to fragments of laminin, fibronectin, procollagen, and EGF have also been described (see, e.g., Cao, 1998, Prog Mol Subcell Biol. 20:161-176). Monoclonal antibodies and cyclic pentapeptides, which block certain integrins that bind RGD proteins (i.e., possess the peptide motif Arg-Gly-Asp), have been demonstrated to have anti-vascularization activities (Brooks et al., 1994, Science 264:569-571; Hammes et al., 1996, Nature Medicine 2:529-533). Moreover, inhibition of the urokinase plasminogen activator receptor by receptor antagonists inhibits angiogenesis, tumor growth and metastasis (Min et al., 1996, Cancer Res. 56: 2428-33; Crowley et al., 1993, Proc Natl Acad Sci. 90:5021-25).

[00188] In another embodiment, a combination therapy of the present disclosure comprises administering an immunomodulatory composition of the present disclosure together with a hormonal treatment modality. Such treatment modalities include the administration of hormonal antagonists (e.g., flutamide, bicalutamide, tamoxifen, raloxifene, leuprolide acetate (LUPRON), LH-RH antagonists), inhibitors of hormone biosynthesis and processing, and steroids (e.g., dexamethasone, retinoids, deltoids, betamethasone, cortisol, cortisone, prednisone, dehydrotestosterone, glucocorticoids, mineralocorticoids, estrogen, testosterone, progestins), vitamin A derivatives (e.g., all-trans retinoic acid (ATRA)); vitamin D3 analogs; antigestagens (e.g., mifepristone, onapristone), and antiandrogens (e.g., cyproterone acetate).

[00189] In another embodiment, an immunomodulatory composition of the present disclosure is used in association with a treatment modality that utilizes polynucleotide

compounds, such as antisense polynucleotides, ribozymes, RNA interference molecules, triple helix polynucleotides and the like.

[00190] In certain embodiments, an immunomodulatory composition of the present disclosure is administered in combination with an immunoregulatory agent. In some embodiments, the immunomodulatory composition is formulated with the immunoregulatory agent. An "immunoregulatory agent" is a substance that suppresses, masks, or enhances the immune system of the subject to whom it is administered. Exemplary agents are those that suppress cytokine production, downregulate or suppress self-antigen expression, or mask the MHC antigens. Examples of such agents include 2-amino-6-aryl-5-substituted pyrimidines (see, U.S. Pat. No. 4,665,077), azathioprine (or cyclophosphamide, if there is an adverse reaction to azathioprine); bromocryptine; glutaraldehyde (which masks the MHC antigens, as described in U.S. Pat. No. 4,120,649); anti-idiotypic antibodies for MHC antigens and MHC fragments; cyclosporin A; steroids such as glucocorticosteroids, e.g., prednisone, methylprednisolone, and dexamethasone; cytokine or cytokine receptor antagonists including anti-interferon-γ, -β, or α antibodies; anti-tumor necrosis factor-a antibodies; anti-tumor necrosis factor-.beta. antibodies; anti-interleukin-2 antibodies and anti-IL-2 receptor antibodies; anti-L3T4 antibodies; heterologous anti-lymphocyte globulin; pan-T antibodies, preferably anti-CD3 or anti-CD4/CD4a antibodies; soluble peptide containing a LFA-3 binding domain; IDO inhibitors; streptokinase; TGF-β; streptodomase; FK506; RS-61443; deoxyspergualin; and rapamycin. Examples of cytokines include, but are not limited to lymphokines, monokines, and traditional polypeptide hormones. Included among the cytokines are growth hormone such as human growth hormone, N-methionyl human growth hormone, and bovine growth hormone; parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prorelaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), glucagon, thyroid stimulating hormone (TSH), and luteinizing hormone (LH); hepatic growth factor; fibroblast growth factor; prolactin; placental lactogen; tumor necrosis factor-α.; mullerian-inhibiting substance; mouse gonadotropin-associated peptide; inhibin; activin; vascular endothelial growth factor; integrin; thrombopoiotin (TPO); nerve growth factors such as NGF-α; platelet-growth factor; transforming growth factors (TGFs) such as TGF-α and TGF-β; insulin-like growth factor-I and -II; erythropoietin (EPO); osteoinductive factors; interferons; colony stimulating factors (CSFs) such as macrophage-CSF (M-CSF); granulocyte-macrophage-CgP (GM-CSP); and granulocyte-CSF (G-CSF); interleukins (ILs) such as IL-1, IL-1a, IL-2, 1L-3, IL-4,

IL-5, IL-6, IL-7, IL-8, IL-9, IL-11, IL-12, IL-15; a tumor necrosis factor such as TNF-α or TNF-β; and other polypeptide factors including LIF and kit ligand (KL). As used herein, the term cytokine includes proteins from natural sources or from recombinant cell culture and biologically active equivalents of the native sequence cytokines. Other examples of immunoregulatory agents include mesalazine, mesalamine, sulfasalazine, sulfasalazine derivatives, anti-histamines, glucocorticoids, epinephrine, theophylline, cromolyn sodium, anti-leukotrienes, anti-cholinergic drugs for rhinitis, anti-cholinergic decongestants, mast-cell stabilizers, monoclonal anti-IgE antibodies.

[00191] In certain embodiments, an immunomodulatory composition of the present disclosure is administered in combination therapy with one or more immunomodulatory agents, e.g., a cytokine. Suitable cytokines include, but are not limited to, interleukin-1 (IL-1), IL-2, IL-3, IL-12, IL-15, IL-18, G-CSF, GM-CSF, thrombopoietin, and γ interferon.

Methods of modulating an anti-bacterial immune response

[00192] The present disclosure provides methods of modulating an immune response to a bacterium or a substance produced by a bacterium, the method comprising administering to an individual in need thereof an effective amount of an immunomodulatory composition of the present disclosure.

[00193] In some cases, a method of the present disclosure of modulating an immune response to a bacterium, or a substance produced by a bacterium, is effective to reduce the number of bacteria (e.g., pathogenic bacteria) in the individual by at least about 25%, at least about 50%, at least about 75%, or at least about 99%, compared to a pre-treatment number of pathogenic bacteria in the individual, or to an extent that the pathogenic bacterium cannot be detected in the individual (e.g., in a biological sample obtained from the individual).

[00194] In some cases, a method of the present disclosure of modulating an immune response to a bacterium, or a substance produced by a bacterium (such as endotoxins, toxins, LPS etc.), is effective to regulate an immune response to a pathogenic bacterium. Pathogenic bacteria include, e.g., Gram positive bacteria, Gram negative bacteria, mycobacteria, etc. Non-limiting examples of pathogenic bacteria include Mycobacteria, Streptococcus, Staphylococcus, Pseudomonas, Salmonella, Neisseria, and Listeria. In some cases, the bacteria is *Neisseria gonorrhea*, *M. tuberculosis*, *M. leprae*, *Listeria monocytogenes*, *Streptococcus pneumoniae*, *S. pyogenes*, *S. agalactiae*, *S. viridans*, *S. faecalis*, *S. aureus*, *S. epidermis*, or *S. bovis*.

[00195] Other examples of pathogenic bacteria contemplated include, but are not limited to, Gram positive bacteria (e.g., Listeria, Bacillus such as *Bacillus anthracis*, Erysipelothrix species), Gram negative bacteria (e.g., Bartonella, Brucella, Burkholderia, Campylobacter, Enterobacter, Escherichia, Francisella, Hemophilus, Klebsiella, Morganella, Proteus, Providencia, Pseudomonas, Salmonella, Serratia, Shigella, Vibrio, and Yersinia species), spirochete bacteria (e.g., Borrelia species including Borrelia burgdorferi that causes Lyme disease), anaerobic bacteria (e.g., Actinomyces and Clostridium species), Gram positive and negative coccal bacteria, Enterococcus species, Streptococcus species, Pneumococcus species, Staphylococcus species, Neisseria species.

[00196] Additional non-limiting examples of specific infectious bacteria include *Citrobacter*, *Chlamydia spp.*, *Helicobacter pyloris*, *Borelia burgdorferi*, *Legionella pneumophila*, *Mycobacteria avium*, *M. intracellulare*, *M. kansaii*, *M. gordonae*, *M. africanum*, *Staphylococcus aureus*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Bacillus anthracis*, *Yersinia pestis*, *Corynebacterium diphtheriae*, *Erysipelothrix rhusiopathiae*, *Clostridium perfringens*, *Clostridium tetani*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Pasturella multocida*, *Fusobacterium nucleatum*, *Streptobacillus moniliformis*, *Treponema pallidium*, *Treponema pertenue*, *Leptospira*, *Rickettsia*, *Porphyromonas gingivalis*, and *Actinomyces israelli*.

[00197] The pathogenic bacteria can be wild-type, viable, inactivated, heat-killed, mutated, attenuated and/or genetically modified.

[00198] In some cases, a method of the present disclosure of modulating an immune response to a bacterium, or a substance produced by a bacterium, comprises administering an immunomodulatory composition to an individual in need thereof, and further comprising administering to the individual an effective amount of an anti-bacterial or an antimycobacterial agent. Anti-bacterial and anti-mycobacterial agents are known in the art and include, e.g., beta-lactam antibiotics, tetracyclines, streptomycin, chloramphenicol, neomycin, gramicidin, bacitracin, sulfonamides, nitrofurazone, nalidixic acid, rifampicin, fluoroquinolones, isoniazid, pyrazinamide, vancomycin, methicillin etc.

[00199] Suitable anti-bacterial agents include, e.g., Aminoglycosides such as Amikacin, Apramycin, Arbekacin, Bambermycins, Butirosin, Dibekacin, Dihdrostreptomycin, Fortimicin(s), Gentamicin, Ispamicin, Kanamycin, Micronomicin, Neomycin, Neomycin Undecylenate, Netilmicin, Paromomycin, Ribostamycin, Sisomicin, Spectinomycin, Streptomycin, Streptonicozid and Tobramycin; Ansamycins such as Rifamide, Rifampin,

Rifamycin and Rifaximin; β-lactams such as Carbapenems such as Imipenem; Cephalosporins such as Cefactor, Cefadroxil, Cefamandole, Cefatrizine, Cefazedone, Cefazolin, Cefixime, Cefinenoxime, Cefodizime, Cefonicid, Cefoperazone, Ceforanide, Cefotaxime, Cefotiam, Cefpimizole, Cefpirimide, Cefpodoxime Proxetil, Cefroxadine, Cefsulodin, Ceftazidime, Cefteram, Ceftezole, Ceftibuten, Ceftizoxime, Ceftriaxone, Cefuroxime, Cefuzonam, Cephacetrile Sodium, Cephalexin, Cephaloglycin, Cephaloridine, Cephalosporin, Cephalothin, Cephapirin Sodium, Cephradine and Pivcefalexin; Cephamycins such as Cefbuperazone, Cefmetazole, Cefminox, Cefetan and Cefoxitin; Monobactams such as Aztreonam, Carumonam and Tigemonam; Oxacephems such as Flomoxef and Moxolactam; Penicillins such as Amidinocillin, Amdinocillin Pivoxil, Amoxicillin, Ampicillan, Apalcillin, Aspoxicillin, Azidocillan, Azlocillan, Bacampicillin, Benzylpenicillinic Acid, Benzylpenicillin Sodium, Carbenicillin, Carfecillin Sodium, Carindacillin, Clometocillin, Cloxacillin, Cyclacillin, Dicloxacillin, Diphenicillin Sodium, Epicillin, Fenbenicillin, Floxicillin, Hetacillin, Lenampicillin, Metampicillin, Methicillin Sodium, Mezlocillin, Nafcillin Sodium, Oxacillin, Penamecillin, Penethamate Hydriodide, Penicillin G Benethamine, Penicillin G Benzathine, Penicillin G Benzhydrylamine, Penicillin G Calcium, Penicillin G Hydrabamine, Penicillin G Potassium, Penicillin G Procaine, Penicillen N, Penicillin O, Penicillin V, Penicillin V Benzathine, Penicillin V Hydrabamine, Penimepicycline, Phenethicillin Potassium, Piperacillin, Pivapicillin, Propicillin, Quinacillin, Sulbenicillin, Talampicillin, Temocillin and Ticarcillin; Lincosamides such as Clindamycin and Lincomycin; Macrolides such as Azithromycin, Carbomycin, Clarithromycin, Erythromycin, Erythromycin Acistrate, Erythromycin Estolate, Erythromycin Glucoheptonate, Erythromycin Lactobionate, Erythromycin Propionate, Erythromycin Stearate, Josamycin, Leucomycins, Midecamycins, Miokamycin, Oleandomycin, Primycin, Rokitamycin, Rosaramicin, Roxithromycin, Spiramycin and Troleandomycin; Polypeptides such as Amphomycin, Bacitracin, Capreomycin, Colistin, Enduracidin, Enviomycin, Fusafungine, Gramicidin(s), Gramicidin S, Mikamycin, Polymyxin, Polymyxin B-Methanesulfonic Acid, Pristinamycin, Ristocetin, Teicoplanin, Thiostrepton, Tuberactinomycin, Tyrocidine, Tyrothricin, Vancomycin, Viomycin, Viomycin Pantothenate, Virginiamycin and Zinc Bacitracin; Tetracyclines such as Apicycline, Chlortetracycline, Clomocycline, Demeclocycline, Doxycycline, Guamecycline, Lymecycline, Meclocycline, Methacycline, Minocycline, Oxytetracycline, Penimepicycline, Pipacycline, Rolitetracycline, Sancycline, Senociclin

and Tetracycline; Cycloserine; Mupirocin; and Tuberin. Suitable anti-bacterial agents include antibodies specific for a bacterium.

Methods of modulating an anti-viral immune response

[00200] The present disclosure provides methods of modulating an immune response to a virus, the method comprising administering to an individual in need thereof an effective amount of an immunomodulatory composition of the present disclosure.

[00201] In some cases, a method of the present disclosure of modulating an immune response to a virus is effective to reduce the number of viruses (e.g., pathogenic viruses) in the individual by at least about 25%, at least about 50%, at least about 75%, or at least about 99%, or to an extent that the pathogenic virus cannot be detected in the individual (e.g., in a biological sample obtained from the individual).

[00202] For example, in some cases, a method of the present disclosure of modulating an immune response to a virus is effective to reduce the viral load in the individual by at least about 25%, at least about 50%, at least about 75%, or at least about 99%, or to an extent that the pathogenic virus cannot be detected in the individual (e.g., in a biological sample obtained from the individual). In some cases, a method of the present disclosure of modulating an immune response to a virus is effective to reduce the number of genome copies of the virus in the individual by at least about 25%, at least about 50%, at least about 75%, or at least about 99%, compared to a pre-treatment number of genome copies of the virus in the individual, or to an extent that no genome copies of the virus can be detected in the individual (e.g., in a biological sample obtained from the individual).

[00203] In some cases, a method of the present disclosure of modulating an immune response to a virus regulates an immune response to a pathogenic virus. Pathogenic viruses include, but are not limited to, herpes viruses (HSV-1, HSV-2, VZV, EBV, CMV, HHV-6, HHV-8), influenza viruses (Flu A, B), hepatitis viruses (HepA, HepB, HepC, HepD, HepE), human immunodeficiency viruses (HIV-1, HIV-2), respiratory syncytial viruses, measles viruses, rhinoviruses, adenoviruses, SARS viruses, papillomaviruses, orthopoxviruses, West Nile viruses, and a dengue viruses. Pathogenic viruses include members of the Flaviviridae family of viruses. Pathogenic viruses include a flavivirus selected from the group consisting of dengue, Kunjin, Japanese encephalitits, West Nile, and yellow fever virus. Pathogenic viruses include lymphocytic choriomenignitis virus, hepatitis B virus, Epstein Barr virus, and human immunodeficiency virus. Pathogenic viruses include, but are not limited to: Retroviridae (e.g. human immunodeficiency viruses, such as HIV-1, also referred to as LAV or HTLV-III/LAV, or HIV-III; and other

isolates, such as HIV-LP; Picornaviridae (e.g. polio viruses, hepatitis A virus; enteroviruses, human Coxsackie viruses, rhinoviruses, echoviruses); Calciviridae (e.g. strains that cause gastroenteritis); Togaviridae (e.g. equine encephalitis viruses, rubella viruses); Flaviridae (e.g. dengue viruses, encephalitis viruses, yellow fever viruses); Coronaviridae (e.g. coronaviruses); Rhabdoviridae (e.g. vesicular stomatitis viruses, rabies viruses); Filoviridae (e.g. ebola-like viruses; Marburg virus); Paramyxoviridae (e.g. parainfluenza viruses, mumps virus, measles virus, respiratory syncytial virus); Orthomyxoviridae (e.g. influenza viruses); Bungaviridae (e.g. Hantaan viruses, bunga viruses, phleboviruses and Nairo viruses); Arenaviridae (hemorrhagic fever viruses); Reoviridae (e.g. reoviruses, orbiviurses and rotaviruses); Bornaviridae; Hepadnaviridae (Hepatitis B virus); Parvoviridae (parvoviruses); Papovaviridae (papilloma viruses, polyoma viruses); Adenoviridae (e.g., adenoviruses); Herpesviridae (herpes simplex virus (HSV) 1 and 2), varicella zoster virus, cytomegalovirus (CMV), herpes virus; Poxviridae (variola viruses, vaccinia viruses, pox viruses); and Iridoviridae (e.g. African swine fever virus); and unclassified viruses (e.g. the etiological agents of Spongiform encephalopathies, the agent of delta hepatitis, thought to be a defective satellite of hepatitis B virus), the agents of non-A, non-B hepatitis (class 1, internally transmitted; class 2, parenterally transmitted, i.e., Hepatitis C Virus); Norwalk and related viruses, and astroviruses.

[00204] In some cases, a method of the present disclosure of modulating an immune response to a virus, comprises administering an immunomodulatory composition to an individual in need thereof, and further comprising administering to the individual an effective amount of at least one additional therapeutic agent, e.g., an anti-viral agent.

[00205] Anti-viral agents are known in the art and include, e.g., an anti-HCV agent such as ribavirin and its analogues; glycosidase inhibitors; glucosidase inhibitors; IRES (internal ribosomal entry site), p7, entry, fusion, helicase, assembly, egress, NS2, NS3, NS4, NS5a and NS5B inhibitors; inosine monophosphate dehydrogenase inhibitors; cyclophilin inhibitors; metalloprotease inhibitors; anti-HCV nucleos(t)ide and non-nucleoside RNA polymerase inhibitors etc.; an anti-HIV agent; anti-HBV agent; and the like.

[00206] In some embodiments, the at least one additional therapeutic agent is an interferon (e.g., interferon-alpha, interferon-beta, interferon-gamma, interferon-lambda, interferon-tau, interferon-omega, etc.). In some embodiments, the at least one additional

therapeutic agent is IFN-α. In some embodiments, the at least one additional therapeutic agent is IFN-β.

[00207] Suitable additional anti-viral agents for treating an HCV infection include, but are not limited to, ribavirin and its prodrugs such as viramidine, telaprevir, sofosbuvir, boceprevir, ciluprevir, simeprevir, danoprevir, vaniprevir, MK-5172, MK-0608, 2'-C-methyl-7-deaza adenosine, 2'-C-methyl-adenosines, BI201335, narlaprevir, asunaprevir, GS-9256, GS-9451, ABT-450, IDX-320, ACH-1625, Valopicitabine, mericitabine, R1626, PSI-938, INX-189, BILN1941, BI-207127, VCH222, VX-135, ANA598, ANA773, ABT-072, ABT-333, HCV-796, GS-9190, Daclatasavir, BMS-824393, BMS-791325, PPI-461, GS-5885, alisporivir (Debio-025), NIM-811, SCY-635, nitazoxanide, clemizole, miravirasen, celgosivir, BCX-5191, GSK-2336805, anti-PD-1 antibodies (CT-011), bavituximab (anti-phosphatidyl serine Mab), therapeutic vaccine (GI-5005, IC-41, TG-4040) prophylactic vaccine (such as HCV E1/E2/MF-59), and the prodrugs thereof. Suitable additional therapeutic agents include, e.g., therapeutic agents for the treatment of an hepatitis B virus infection include, but are not limited to lamivudine, adefovir, entecavir, telbuvudine, tenofovir and the prodrugs thereof.

[00208] For example, suitable additional anti-viral agents for treating an HCV infection include weekly injections of pegylated IFN-α combined with twice-daily oral doses of ribavirin (1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide).

[00209] Suitable additional therapeutic agents include, e.g., therapeutic agents for the treatment of an immunodeficiency virus infection, or for the treatment of a disorder that may accompany an immunodeficiency virus infection (e.g., a bacterial infection, a fungal infection, and the like). Suitable additional therapeutic agents include, e.g., beta-lactam antibiotics, tetracyclines, chloramphenicol, neomycin, gramicidin, bacitracin, sulfonamides, nitrofurazone, nalidixic acid, cortisone, hydrocortisone, betamethasone, dexamethasone, fluocortolone, prednisolone, triamcinolone, indomethacin, sulindac, acyclovir, amantadine, rimantadine, recombinant soluble CD4 (rsCD4), cyanovirin-N, microvirin, fuzeon, anti-receptor antibodies (e.g., for rhinoviruses), nevirapine, cidofovir (Vistide™), trisodium phosphonoformate (Foscarnet™), famcyclovir, pencyclovir, valacyclovir, nucleic acid/replication inhibitors, interferon, zidovudine (AZT, Retrovir™), didanosine (dideoxyinosine, ddI, Videx™), stavudine (d4T, Zerit™), zalcitabine (dideoxycytosine, ddC, Hivid™), nevirapine (Viramune™), lamivudine (Epivir™, 3TC), protease inhibitors, saquinavir (Invirase™, Fortovase™), ritonavir (Norvir™), nelfinavir (Viracept™), efavirenz (Sustiva™), abacavir (Ziagen™),

amprenavir (Agenerase™) indinavir (Crixivan™), ganciclovir, AzDU, delavirdine (Rescriptor™), kaletra, trizivir, rifampin, clathiromycin, erythropoietin, colony stimulating factors (G-CSF and GM-CSF), non-nucleoside reverse transcriptase inhibitors, nucleoside inhibitors, viral entry inhibitors, fusion inhibitors, integrase inhibitors, adriamycin, fluorouracil, methotrexate, asparaginase and combinations thereof. Additional suitable therapeutic agents for HIV include integrase and fusion inhibitors such as Raltegravir, Elvitegravir, Enfuvirtide, Maraviroc etc.

[00210] In some embodiments, the at least one additional therapeutic agent is a neuraminidase inhibitor, e.g., where the influenza virus is influenza A or influenza B. Suitable neuraminidase inhibitors include, e.g., oseltamivir (ethyl (3*R*,4*R*,5*S*)-5-amino-4-acetamido-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate; Tamiflu™), zanamivir (2*R*,3*R*,4*S*)- 4-[(diaminomethylidene)amino]- 3-acetamido- 2-[(1*R*,2*R*)- 1,2,3-trihydroxypropyl]- 3,4-dihydro-2*H*-pyran-6-carboxylic acid; Relenza™), and peramivir (1*S*,2*S*,3*S*,4*R*)-3-[(1*S*)-1-acetamido-2-ethyl-butyl]-4-(diaminomethylideneamino)-2-hydroxy-cyclopentane-1-carboxylic acid). In some embodiments, the at least one additional therapeutic agent is an M2 blocker, e.g., blocks a viral ion channel (M2 protein). The antiviral drugs amantadine and rimantadine are M2 blockers, and can be used in subject method.

[00211] Suitable additional therapeutic agents, e.g., for the treatment of an HSV-1 or an HSV-2 infection include, but are not limited to, acyclovir (Zovirax), valganciclovir, famciclovir, valacyclovir (Valtrex), ganciclovir (Cytovene), cidofovir (Vistide), antisense oligonucleotide fomivirsen (Vitravene), foscarnet (Foscavir), penciclovir, idoxuridine, vidarabine, and trifluridine.

[00212] In some embodiments, the one or more different therapeutic agent is selected antiviral agents that target two or more different viruses; e.g., an HIV inhibitor, HBV inhibitor, HCV inhibitor, herpes virus inhibitor, influenza virus inhibitor, RNA inhibitor, interfering RNA (RNAi) inhibitor, natural products etc. In some cases, a method of the present disclosure of treating a viral infection comprises administering an immunomodulatory composition to an individual in need thereof, and further comprising administering to the individual an effective amount of at least one additional therapeutic agent, e.g., a monoclonal antibody or antibody products directed against viral antigens, where suitable monoclonal antibodies include but are not limited to HBIg, antibodies against influenza virus strains, anti-hepatitis A virus antibody, SYNAGIS (anti-RSV Mab), anti-rabies antibody, ostavir (anti-HBV Mab), Pro542 (anti-HIV gp120), Potovir

(anti-CMV Mab), anti-PD-1 antibodies (CT-011), bavituximab (anti-phosphatidyl serine Mab) etc.

Methods of modulating an immune response to a parasitic infection

[00213] The present disclosure provides methods of modulating an immune response to a microbial parasite (e.g., a pathogenic protozoan; a helminth; etc.), the method comprising administering to an individual in need thereof an effective amount of an immunomodulatory composition of the present disclosure.

[00214] In some cases, a method of the present disclosure of modulating an immune response to a microbial parasite is effective to reduce the number of microbial parasites (e.g., pathogenic protozoa; pathogenic helminths) in the individual by at least about 25%, at least about 50%, at least about 75%, or at least about 99%, compared to a pre-treatment number of microbial parasite in the individual, or to an extent that the microbial parasite cannot be detected in the individual (e.g., in a biological sample obtained from the individual).

[00215] In some cases, a method of the present disclosure of modulating an immune response to a microbial parasite comprises administering an immunomodulatory composition to an individual in need thereof, and further comprising administering to the individual an effective amount of a least one additional therapeutic agent. Anti-parasitic agents are known in the art and include, e.g., chloroquine, etc. For example, anti-malarial agents include, e.g., quinine, chloroquine, atovaquone, proguanil, primaquine, amodiaquine, mefloquine, piperaquine, artemisinin, methylene blue, pyrimethamine, sulfadoxine, artemether-lumefantrine, dapsone-chlorproguanil, artesunate, quinidine, clopidol, pyridine/pyridinol analogs, 4(1H)-quinolone analogs, dihydroartemisinin, a mixture of atovaquone and proguanil, an endoperoxide, and an acridone. Anti-parasitic agents include antibodies specific for the parasite.

[00216] In some cases, a method of the present disclosure of modulating (e.g., reducing) an immune response to a microbial parasite modulates an immune response to a microbial parasite such as Plasmodium spp., *Toxoplasma gondii*, Babesia spp., *Trichinella spiralis*, *Entamoeba histolytica*, *Giardia lamblia*, *Enterocytozoon bieneusi*, Naegleria, Acanthamoeba, *Trypanosoma rhodesiense* and *Trypanosoma gambiense*, Isospora spp., Cryptosporidium spp, Eimeria spp., Neospora spp., Sarcocystis spp., and Schistosoma spp.

[00217] In some cases, a method of the present disclosure of modulating (e.g., reducing) an immune response to a protozoan parasite modulates an immune response to a

protozoan parasite such as Giardia; a plasmodium species (e.g., *Plasmodium falciparum*); *Toxoplasma gondii*; a cryptosporidium; a Trichomonas species; a trypanosome (e.g., *Trypanosoma cruzi*); or Leishmania.

Methods of modulating an immune response to a pathogenic fungus

[00218] The present disclosure provides methods of modulating an immune response to a pathogenic fungus, the method comprising administering to an individual in need thereof an effective amount of an immunomodulatory composition of the present disclosure.

[00219] In some cases, a method of the present disclosure of modulating an immune response to a pathogenic fungus is effective to reduce the number of fungal bodies in the individual by at least about 25%, at least about 50%, at least about 75%, or at least about 99%, compared to a pre-treatment number of fungal bodies in the individual, or to an extent that the pathogenic fungus cannot be detected in the individual (e.g., in a biological sample obtained from the individual).

[00220] In some cases, a method of the present disclosure of modulating (e.g., reducing) an immune response to a pathogenic fungus induces or modulates an immune response to a fungus such as Candida spp. including *C. albicans*, Aspergillus spp., Cryptococcus spp. including *C. neoformans*, Blastomyces sp., Pneumocytes spp., or Coccidioides spp.

[00221] In some cases, a method of the present disclosure of modulating an immune response to a pathogenic fungus comprises administering an immunomodulatory composition to an individual in need thereof, and further comprising administering to the individual an effective amount of a least one additional therapeutic agent. Anti-fungal agents are known in the art and include, e.g., flucanazole, 5-fluorocytosine, etc.

[00222] Suitable anti-fungal agents include, e.g., Polyenes such as Amphotericin-B (including various formulations of Amphotericin-B), Candicidin, Dermostatin, Filipin, Fungichromin, Hachimycin, Hamycin, Lucensomycin, Mepartricin, Natamycin, Nystatin, Pecilocin and Perimycin; and others such as Azaserine, Griseofulvin, Oligomycins, Neomycin Undecylenate, Pyrrolnitrin, Siccanin, Tubercidin and Viridin; Allylamines such as Naftifine and Terbinafine; Imidazoles such as Bifonazole, Butoconazole, Chlordantoin, Chlormidazole, Cloconazole, Clotrimazole, Econazole, Enilconazole, Fenticonazole, Isoconazole, Ketoconazole, Miconazole, Omoconazole, Oxiconazole, Nitrate, Sulconazole and Tioconazole; Triazoles such as Fluconazole, Itraconazole and Terconazole; and other others such as Acrisorcin, Amorolfine, Biphenamine, Bromosalicylchloranilide, Buclosamide, Calcium Propionate, Chlophenesin, Ciclopirox, Cloxyquin, Coparaffinate, Diamthazole, Dihydrochloride, Exalamide, Flucytosine,

Halethazole, Hexetidine, Loflucarban, Nifuratel, Potassium Iodide, Propionic Acid, Pyrithione, Salicylanilide, Sodium Propionate, Sulbentine, Tenonitrozole, Tolciclate, Tolindate, Tolnaftate, Tricetin, Ujothion, Undecylenic Acid and Zinc Propionate.

Methods of treating an allergic disease

[00223] The present disclosure provides methods of treating an allergic disease such as asthma, allergic rhinitis, conjunctivitis, atopic dermatitis in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of the present disclosure. In some cases, a method of the present disclosure of treating an allergic disease comprises administering to an individual in need thereof an effective amount of an immunomodulatory composition of the present disclosure, where the immunomodulatory composition comprises an allergen. Suitable allergens are described above.

[00224] In some cases, a subject a method of the present disclosure of treating an allergic disease is effective to regulate an immune response. In some cases, a subject a method of the present disclosure of treating an allergic disease is effective to decrease one or more of: a) the level of IgE in an individual; b) the level of allergen-specific IgE in an individual; c) the number of mast cells in the individual; d) the level of histamine in the individual; and e) the level of IL-4 in the individual, compared to a pre-treatment level.

[00225] In some cases, a method of the present disclosure of treating an allergic disease comprises administering an immunomodulatory composition to an individual in need thereof, and further comprising administering to the individual an effective amount of at least one additional therapeutic agent. Suitable additional therapeutic agents include, e.g., anti-histamines, steroids (e.g., corticosteroids), prostaglandin inducers, anti-inflammatory agents, leukotriene antagonists, IL-4 muteins, soluble IL-4 receptors, immunosuppressants (such as tolerizing peptide vaccine), anti-IL-4 antibodies, IL-4 antagonists, anti-IL-5 antibodies, soluble IL-13 receptor-Fc fusion proteins, anti-IL-9 antibodies, CCR3 antagonists, CCR5 antagonists, VLA-4 inhibitors, and downregulators of IgE. Suitable steroids include, but are not limited to, beclomethasone, fluticasone, tramcinolone, budesonide, corticosteroids and budesonide.

Methods of treating an autoimmune disorder

[00226] The present disclosure provides methods of treating an autoimmune disorder in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of the present disclosure. Autoimmune conditions account for many autoimmune disorders such as rheumatoid arthritis, asthma, type 1

diabetes, multiple sclerosis, systemic lupus erythrymatosus (SLE), Sjorgen's syndrome, atherosclerosis, autoimmune hepatitis, autoimmune pancreatitis, celiac disease, autoimmune hemolytic anemia, ankylosing spondylitis, autoimmune disease associated cancers, autoimmune disease associated fibrosis, etc. By modulating innate and adaptive immune mechanisms through the immunomodulatory composition of the present disclosure, autoimmune disorders can be treated. In some cases, a method of the present disclosure of treating an autoimmune disorder comprises administering to an individual in need thereof an effective amount of an immunomodulatory composition of the present disclosure, where the immunomodulatory composition comprises an autoantigen. Suitable autoantigens are described above.

[00227] In some cases, a subject a method of the present disclosure of treating an autoimmune disorder is effective to reduce the number and/or activity of self-reactive T cells in an individual by at least about 25%, at least about 50%, at least about 75%, or at least about 99% compared to a pre-treatment number and/or activity of self-reactive T cells, or to an extent that self-reactive T cells cannot be detected in the individual (e.g., in a biological sample obtained from the individual).

[00228] In some cases, a subject a method of the present disclosure of treating an autoimmune disorder is effective to reduce the level of autoantibodies in an individual by at least about 25%, at least about 50%, at least about 75%, or at least about 99% compared to a pre-treatment level of autoantibodies, or to an extent that autoantibodies cannot be detected in the individual (e.g., in a biological sample obtained from the individual).

[00229] In some cases, a subject a method of the present disclosure of treating an autoimmune disorder is effective to modulate the level of cytokines in an individual by at least about 25%, at least about 50%, at least about 75%, or at least about 99% compared to a pre-treatment level of cytokines, or to an extent that cytokines cannot be detected in the individual (e.g., in a biological sample obtained from the individual).

[00230] In some cases, a method of the present disclosure of treating an autoimmune disorder comprises administering an immunomodulatory composition to an individual in need thereof, and further comprising administering to the individual an effective amount of a least one additional therapeutic agent. Examples of therapeutic agents that can be used to treat autoimmune disorders include, but are not limited to, anti-inflammatory agents; immunosuppressive agents (e.g., corticosteroids (e.g., prednisone, cortisol, methylprednisolone, etc.)), cyclosporin A); cytotoxic agents (e.g., 6-mercaptopurine,

azathioprine, methotrexate, alkylating agents anti-metabolite agents); plant alkaloids; natural products; steroid hormones; hypoxic agents; anti-proliferative agents; anticancer agents; danazol; colchisine; levamisole; biological response modifiers and the like.

[00231] Examples of therapeutic agents that can also be used to treat autoimmune disorders include agents that act to reduce cellular proliferation are known in the art and widely used. Such agents include alkylating agents, such as nitrogen mustards, nitrosoureas, ethylenimine derivatives, alkyl sulfonates, and triazenes, including, but not limited to, mechlorethamine, cyclophosphamide (Cytoxan.TM.), melphalan (L-sarcolysin), carmustine (BCNU), lomustine (CCNU), semustine (methyl-CCNU), streptozocin, chlorozotocin, uracil mustard, chlormethine, ifosfamide, chlorambucil, pipobroman, triethylenemelamine, triethylenethiophosphoramine, busulfan, dacarbazine, and temozolomide.

[00232] Antimetabolite agents include folic acid analogs, pyrimidine analogs, purine analogs, and adenosine deaminase inhibitors, including, but not limited to, cytarabine (CYTOSAR-U), cytosine arabinoside, fluorouracil (5-FU), floxuridine (FudR), 6-thioguanine, 6-mercaptopurine (6-MP), pentostatin, 5-fluorouracil (5-FU), methotrexate, 10-propargyl-5,8-dideazafolate (PDDF, CB3717), 5,8-dideazatetrahydrofolic acid (DDATHF), leucovorin, fludarabine phosphate, pentostatine, gemcitabine, cyclocytidine, guanazole, inosine glycodialdehyde, EICAR, ribavirin, tiazofurin, defroxamine and pyrazoloimidazole.

[00233] Suitable natural products and their derivatives, (e.g., vinca alkaloids, antitumor antibiotics, enzymes, lymphokines, and epipodophyllotoxins), include, but are not limited to, Ara-C, paclitaxel (Taxol®), docetaxel (Taxotere®), deoxycoformycin, mitomycin-C, L-asparaginase, azathioprine; brequinar; alkaloids, e.g. vincristine, vinblastine, vinorelbine, vindesine, etc.; podophyllotoxins, e.g. etoposide, teniposide, camptothecin etc.; antibiotics, e.g. anthracycline, daunorubicin hydrochloride (daunomycin, rubidomycin, cerubidine), idarubicin, doxorubicin, epirubicin and morpholino derivatives, etc.; phenoxizone biscyclopeptides, e.g. dactinomycin; basic glycopeptides, e.g. bleomycin; anthraquinone glycosides, e.g. plicamycin (mithramycin); anthracenediones, e.g. mitoxantrone; azirinopyrrolo indolediones, e.g. mitomycin; macrocyclic immunosuppressants, e.g. cyclosporine, FK-506 (tacrolimus, prograf), rapamycin, etc.; antivascular flavonoids; and the like. Other agents include minerals, nutrients, vitamins, supplements, anti-oxidants, herbs, spices (ginger, oregano, clove etc),

natural health products (green tea, fish oil etc) and anti-inflammatory treatments and modalities.

[00234] Other anti-proliferative cytotoxic agents are navelbene, CPT-11, anastrazole, letrazole, capecitabine, reloxafine, cyclophosphamide, folic acid, retinoic acid, ifosamide, and droloxafine. Other suitable anti-proliferative agents include siRNA, interfering RNA (RNAi), and anti-sense RNA.

[00235] Microtubule affecting agents that have antiproliferative activity are also suitable for use and include, but are not limited to, allocolchicine (NSC 406042), Halichondrin B (NSC 609395), colchicine (NSC 757), colchicine derivatives (e.g., NSC 33410), dolstatin 10 (NSC 376128), maytansine (NSC 153858), rhizoxin (NSC 332598), paclitaxel (Taxol®), Taxol® derivatives, docetaxel (Taxotere®), thiocolchicine (NSC 361792), trityl cysterin, vinblastine sulfate, vincristine sulfate, natural and synthetic epothilones including but not limited to, eopthilone A, epothilone B, discodermolide; estramustine, nocodazole, and the like.

[00236] Hormone modulators and steroids (including synthetic analogs) that are suitable for use include, but are not limited to, adrenocorticosteroids, e.g. prednisone, dexamethasone, etc.; estrogens and pregestins, e.g. hydroxyprogesterone caproate, medroxyprogesterone acetate, megestrol acetate, estradiol, clomiphene, tamoxifen; etc.; and adrenocortical suppressants, e.g. aminoglutethimide; 17α-ethinylestradiol; diethylstilbestrol, testosterone, fluoxymesterone, dromostanolone propionate, testolactone, methylprednisolone, methyl-testosterone, prednisolone, triamcinolone, chlorotrianisene, hydroxyprogesterone, aminoglutethimide, estramustine, medroxyprogesterone acetate, leuprolide, Flutamide (Drogenil), Toremifene (Fareston), and Zoladex®. Estrogens stimulate proliferation and differentiation; therefore, compounds that bind to the estrogen receptor are used to block this activity. Corticosteroids may inhibit T cell proliferation.

[00237] Other cytotoxic agents include metal complexes, e.g. cisplatin (cis-DDP), carboplatin, etc.; ureas, e.g. hydroxyurea; and hydrazines, e.g. N-methylhydrazine; epidophyllotoxin; a topoisomerase inhibitor, e.g., irinotecan, etopside phosphate, mitoxantrone ; procarbazine; mitoxantrone; leucovorin; tegafur; etc. Other anti-proliferative agents of interest include immunosuppressants, e.g. mycophenolic acid, thalidomide, desoxyspergualin, azasporine, leflunomide, mizoribine, azaspirane (SKF 105685); Iressa® (ZD 1839, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-(3-(4-morpholinyl)propoxy)quinazoline); etc.

[00238] Biological response modifiers suitable for use in connection with the methods of the present disclosure include, but are not limited to, (1) inhibitors of tyrosine kinase (RTK) activity; (2) inhibitors of serine/threonine kinase activity; (3) tumor-associated antigen antagonists, such as antibodies that bind specifically to a tumor antigen; (4) apoptosis receptor agonists; (5) interleukin-2; (6) interferon-α.; (7) interferon -γ; (8) colony-stimulating factors; (9) inhibitors of angiogenesis; (10) antagonists of tumor necrosis factor; and (11) BRAF inhibitors.

Methods of treating diseases comprising an immune dysregulation

[00239] The present disclosure provides methods of modulating, restoring and/or regulating an immune dysfunction in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of the present disclosure. Immune dysfunction conditions account for many diseases such as rheumatoid arthritis (RA) and related diseases, diabetes, psoriasis, systemic lupus erythematosus (SLE) and related diseases, graft-versus-host disease (GVHD), ulcerative colitis, bacterial-induced colitis, Crohn's disease, Alopecia areata, asthma, allergic rhinitis, conjunctivitis, transplant rejection, Hashimoto's thyroiditis, inflammatory bowel diseases (IBD), short bowel syndrome and other gastrointestinal disorders (such as Crohn's disease, ulcerative colitis), cardiovascular diseases, obesity, wound healing, burn recovery, aging, weight gain, fat deposition, etc. Dysregulation of immune responses at the gut mucosal surface can cause systemic immune activation through increased translocation of microbes and microbial products from the intestinal tract. By modulating innate and adaptive immune mechanisms (including immune cells, cytokines, antibodies etc.) through the immunomodulatory composition of the present disclosure, immune dysregulation can be prevented and/or treated.

[00240] In some cases, a method of the present disclosure of treating an immune dysfunction disorder comprises administering an immunomodulatory composition to an individual in need thereof, and further comprising administering to the individual an effective amount of at least one additional therapeutic agent.

[00241] In some cases, the method comprising administering to an individual in need thereof an effective amount of an immunomodulatory composition of the present disclosure in a vaccine including an antigen that will modulate the dysfunctional immune response to a disease related antigen.

[00242] In some cases, the method comprising administering to an individual in need thereof, an effective amount of an immunomodulatory composition of the present

disclosure in protecting, modulating, restoring or correcting disease- or medical condition-related imbalances in the patients' microbiome. Dysbalance in microbiota accounts for various disorders such as dermatological conditions, exuberant inflammatory responses, inflammation associated cancers, preterm birth, infertility, female contraception, urogenital infections, sexually transmitted diseases etc.

[00243] Another aspect of the invention includes method of treatment by substantially increasing or decreasing a relative abundance of miocrobiota of the subject.

[00244] In some cases, a method of the present disclosure of treating an immune dysregulation and restoring homeostasis comprises administering an immunomodulatory composition to an individual in need thereof, and further comprising administering to the individual an effective amount of one or more members of the microbiome or a probiotic.

Methods of treating diseases comprising an undesirable inflammatory activity

[00245] The present disclosure provides methods of modulating and/or regulating an undesirable inflammatory activity in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of the present disclosure. Undesirable inflammatory conditions account for many diseases such as diarrhoeal disease, mucositis due to chemotherapy or radiotherapy, gastroenteritis due to an infectious agent or an antibiotic agent, pouchitis, obesity related inflammation, appendicitis, organ (liver, kidney, lung, heart, islets etc.) transplantation, bacterial infections, viral infections, fungal infections, cancer-associated inflammation, urogenital diseases, bacterial vaginosis, surgical associated trauma, sepsis, anorexia, hyperoxalurea, ulcers, wound healing, renal disease, hepatic diseases, liver fibrosis, alcoholic hepatitis, fibrotic diseases such as lung fibrosis, kidney fibrosis, idiopathic pulmonary fibrosis, acne, undesirable respiratory inflammatory activity, inflammation-associated cancers, inflammation-associated organ (lung, liver, kidney, heart, gastrointestinal tract, brain etc.) damage and injury, autoinflammatory diseases (such as TNF receptor associated periodic syndrome, Dubin Johnson syndrome, Behcet's disease, familial mediteranean fever etc.) etc. By modulating innate and adaptive immune mechanisms (including immune cells, cytokines, chemokines, antibodies etc.) through the immunomodulatory composition of the present disclosure, inflammatory disorders can be prevented and/or treated.

[00246] In one aspect of the invention, controlling undesirable inflammatory responses also include modulation in the levels of hormones, prostaglandins, reactive intermediates and leukotrienes.

[00247] In some cases, a method of the present disclosure of treating an inflammatory disorder comprises administering an immunomodulatory composition to an individual in need thereof, and further comprising administering to the individual an effective amount of at least one additional therapeutic agent, one or more members of the microbiome or a probiotic. Examples of therapeutic agents that can be used to treat inflammatory conditions include, but are not limited to, anti-inflammatory agents; immunosuppressive agents; cytotoxic agents and the like.

[00248] Other nonlimiting examples of therapeutic agents that can be used to treat inflammatory conditions include; calcineurin inhibitors (e.g., pimecrolimus, tacrolimus, etc.), methotrexate, cyclosporine and topical agents (e.g., tazarotene, anthralin, calciprotriene, corticosteroids, etc.).

[00249] In some cases, the method comprising administering to an individual in need thereof an effective amount of an immunomodulatory composition of the present disclosure in a vaccine including an antigen that will modulate the inflammatory immune response to a disease related antigen.

[00250] Other examples of autoimmune diseases, immune dysregulation, inflammation, allergic diseases, dermal diseases, infectious diseases, and organ transplantations for which the composition is useful for treatment include diseases such as, primary sclerosis polingitis, sprue, autoimmune arthritis, Lyme arthritis, psoriatic arthritis, reactive arthritis, spondyloarthropathy, dermatitis scleroderma, sarcoidosis, disseminated intravascular coagulation, Kawasaki's disease, nephrotic syndrome, chronic fatigue syndrome, fibromyalgia, Wegener's granulomatosis, Henoch-Schoenlejn purpurea, microscopic vasculitis of the kidneys, chronic active hepatitis, uveitis, septic shock, toxic shock syndrome, sepsis syndrome, cachexia, acquired immunodeficiency syndrome, acute transverse myelitis, Huntington's chorea, primary biliary cirrhosis, hemolytic anemia, polyglandular deficiency type I syndrome and polyglandular deficiency type II syndrome, Schmidt's syndrome, adult (acute) respiratory distress syndrome, seronegative arthopathy, arthropathy, Reiter's disease, psoriatic arthropathy, chlamydia, yersinia and salmonella associated arthropathy, spondyloarhopathy, atheromatous disease/arteriosclerosis, allergic colitis, atopic allergy, food allergies such as peanut allergy, tree nut allergy, egg allergy, milk allergy, soy allergy, wheat allergy, seafood allergy, shellfish allergy, or sesame seed allergy, autoimmune bullous disease, pemphigus vulgaris, pemphigus foliaceus, pemphigoid, 1inear IgA disease, autoimmune haemolytic anaemia, Coombs positive haemolytic anaemia, acquired pernicious anaemia, juvenile

pernicious anaemia, myalgic encephalitis/Royal Free Disease, autoimmune encephalomyelitis, chronic mucocutaneous candidiasis, giant cell arteritis, nonalcoholic fatty liver disease, steatohepatitis, primary sclerosing hepatitis, cryptogenic autoimmune hepatitis, Acquired Immunodeficiency Related Diseases, Hepatitis C, common varied immunodeficiency (common variable hypogammaglobulinaemia), dilated cardiomyopathy, fibrotic lung disease, cryptogenic fibrosing alveolitis, postinflammatory interstitial lung disease, interstitial pneumonitis, connective tissue disease associated interstitial lung disease, mixed connective tissue disease associated lung disease, systemic sclerosis associated interstitial lung disease, Sjogren's disease associated lung disease, ankylosing spondy litis associated lung disease, vasculitic diffuse lung disease, haemosiderosis associated lung disease, drug-induced interstitial lung disease, radiation fibrosis, bronchiolitis obliterans, chronic eosinophilic pneumonia, lymphocytic infiltrative lung disease, postinfectious interstitial lung disease, gouty arthritis, type-l autoimmune hepatitis (classical autoimmune or lupoid hepatitis), type-2 autoimmune hepatitis (anti-LKM antibody hepatitis), autoimmune mediated hypoglycemia, type B insulin resistance with acanthosis nigricans, hypoparathyroidism, osteoarthrosis, primary sclerosing cholangitis, idiopathic leucopenia, autoimmune neutropenia, renal disease NOS, glomerulonephritides, microscopic vasulitis of the kidneys, discoid lupus, erythematosus, male infertility idiopathic or NOS, sperm autoimmunity, sympathetic ophthalmia, pulmonary hypertension secondary to connective tissue disease, Goodpasture's syndrome, pulmonary manifestation of polyarteritis nodosa, acute rheumatio fever, rheumatoid spondylitis, Still's disease, systemic sclerosis, Takayasu's disease/arteritis, autoimmune thrombocytopenia, idiopathic thrombocytopenia, autoimmune thyroid disease, hyperthyroidism, atrophic autoimmune hypothyroidism, primary myxoedema, phacogenic uveitis, primary vasculitis, vitiligo, anaphylaxis, pet allergies, latex allergies, drug allergies, allergic rhinoconjuctivitis, eosinophilic esophagitis, hypereosinophilic syndrome, eosinophilic gastroenteritis cutaneous lupus erythematosus, eosinophilic esophagitis, hypereosinophilic syndrome, eosinophilic gastroenteritis, periodontal diseases such as chronic gingivitis and periodontitis, genitourinary disorders (such as glomerulonephritis, polycystic kidney disease, hydronephrosis, kidney failure, urinary tract obstruction, hyperuricemia etc.), gynaecological disorders (such as vulvodynia, vaginitis, pelvic disorders etc.), reproductive diseases, urological diseases, mitochondria related disorders, pain, migrane, haematological diseases, psychiatric disorders, mouth diseases (such as foot and mouth

disease), musculoskeletol diseases, ocular diseases, renal disorders (such as nephropathic cystinosis), intoxication (such as alcohol intoxication, chronic salicylate intoxication), skin-pruritus, skin-keratosis, skin diseases (such as erythematosquamous, hypertrophic skin disease, popular skin disease, rosacea, pigment disorder, purpura, acne, skin allergy, vitiligo, bullous skin disease, epidermolysis, scleroderma, eczema, cutaneous lymphoma) muscle wasting disease, muscle disorders, bronchus diseases, vascular diseases, uterine fibroids, hormonal imbalance (such as chronic fatigue syndrome), hair loss, osteoporosis, upper respiratory tract infections-associated inflammation, and Paget's disease.

Methods of treating metabolic disorders

[00251] The present disclosure provides methods of treating metabolic disorders in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of the present disclosure. Metabolic disorders account for many diseases such as obesity related metabolic dysfunction, diabetes mellitus, insulin resistance, glucose metabolism disorders, hypoinsulinemia, atherosclerosis, hypercholesterolemia, ischemia, metabolic syndrome, oxidative stress, hypertension, endocrine disorders (Addison's disease, Cushing's disease, hyperthyroidism, hypothyroidism, hypopituitarism, polycystic ovary syndrome etc.), abnormal lipid metabolism, obesity related disorders (such as bone loss, weight gain etc.), pancreas related disorders, mitochondrial disease etc. By modulating innate and adaptive immune mechanisms (including immune cells, cytokines, antibodies etc.) through the immunomodulatory composition of the present disclosure, metabolic diseases can be prevented and/or treated.

[00252] In some cases, a method of the present disclosure of treating an inflammatory disorder comprises administering an immunomodulatory composition to an individual in need thereof, and further comprising administering to the individual an effective amount of at least one additional therapeutic agent, one or more members of microbiome or a probiotic. For example, therapeutic agents of interest include and are not limited to those that are anti-inflammatory agents for the treatment of cardiovascular disease. Such agents include amlodipine, used to lower blood pressure and prevent chest pain; enalapril, used in the treatment of hypertension, and some types of chronic heart failure; pravastatin, atorvastatin and rosuvastatin, used for the treatment of dyslipidemia and the prevention of cardiovascular disease; angiotensin-converting enzyme (ACE) inhibitors (e.g., benazepril, ramipiril, etc.); angiotensin II receptor blockers (ARBs) (e.g., candesartan, losartan, etc.); beta blockers (e.g., acebutolol, bisoprolol, sotalol, etc.); calcium channel

blockers (e.g., amlodipine, verapamil, etc.) etc. Other examples of therapeutic agents of interest include and are not limited to those that are anti-inflammatory agents for the treatment of diabetes. Such agents include agents that target the IKK-NF-κB pathway; etanercept, infliximab, adalimumab, which target TNF-α; anakinra and canakinumab which target IL-1β; tocilizumab which targets IL-6; AMP-activated protein kinase activators; sirtuin-1 activators; mammalian target of rapamycin inhibitors; C-C motif chemokine receptor 2 antagonists, etc. In some cases, therapeutic agents of interest include and are not limited to those that are anti-inflammtory agents for the treatment of obesity. Such agents include lorcaserin; Qsymia™ (Vivus); liraglutide, bupropion, naltrexone, lorcaserin, orlistat, phentermine/topiramate etc.

[00253] In some cases, therapeutic agents of interest include and are not limited to those that are used to treat metabolic disorders such as diabetes include Insulin (e.g., short-, rapid, intermediate and long-acting insulin), amylinomimetic drugs (e.g., pramlinitide), alpha-glucosidase inhibitors (e.g., acarbose, miglitol, etc.), biguanides (e.g., metformin, etc.), sulfonylureas (e.g., glyburide, glipizide, etc.), meglitinides (e.g., repaglinide,), D-phenylalanine derivatives (e.g., nateglinide), thiazolidinediones (e.g., rosiglitazone, pioglitazone, etc.), DPP-4 inhibitors (e.g. itagliptin, saxagliptin, linagliptin, etc.), glucagon-like receptor-1 (GLP-1) agonists (e.g., exenatide, liraglutide, etc.), sodium glucose transporter-2 (SGLT-2) inhibitors (e.g., canagliflozin, dapagliflozin, etc.) etc.

Methods of treating neurological disorders

[00254] The present disclosure provides methods of modulating and/or regulating an inflammatory response, the method comprising administering to an individual in need thereof an effective amount of an immunomodulatory composition of the present disclosure. Inflammatory conditions account for many neurological disorders such as Alzheimer's, depression, attention deficit hyperactive disorder (ADHD), mood disorders, schizophrenia, multiple sclerosis, Parkinson's disease, autism, Amyotrophic Lateral Sclerosis (ALS), Cerebral malaria disorders, Huntington's disease, anxiety disorders, epilepsy, etc. By modulating innate and adaptive immune mechanisms (including immune cells, cytokines, antibodies etc.) through the immunomodulatory composition of the present disclosure, neurological disorders can be treated.

[00255] In some cases, a method of the present disclosure of treating a neurological disorder comprises administering an immunomodulatory composition to an individual in need thereof, and further comprising administering to the individual an effective amount of at least one additional therapeutic agent, one or more members of the microbiome or a

probiotic. Non-limiting examples of disease modifying agents for neurological disorders of interest include, acetylcholinesterase inhibitors (e.g., donepezil, rivastigmine, etc.), N-methyl, D-aspartate receptor (NMDAR) antagonists (e.g., memantine, neramexane, etc.), dopaminergic (e.g., carbidopa/Levodopa), dopamine agonists (e.g. pramipexole, ropinirole, apomorphine, etc.), anticholinergics (e.g., trihexyphenidyl, benztropine mesylate, etc.), catechol-o-methyltransferase (COMT) inhibitors (e.g. entacapone, tolcapone, etc.), anti-convulsants (e.g. diazepam, baclofen, dantrolene, tizanidine, etc.), disease modifying agents; (e.g., teriflunomide, fingolimod, mitoxantrone, dimethyl fumarate, natalizumab, etc.).

[00256] In some cases, the method comprising administering to an individual in need thereof an effective amount of an immunomodulatory composition of the present disclosure in a vaccine including an antigen that will modulate an immune response to a disease related protein such as the amyloid plaques characteristics of Alzheimer or Creutzfeldt-Jacob disease (CJD).

Methods of preventing or treating immunosuppression and infections

[00257] The present disclosure provides methods of preventing or limiting immune defect/deficiency/suppression due to viral infections or due to infections following strokes and other brain injuries comprising administering an immunomodulatory composition of the present disclosure to an individual in need thereof. Various forms of viral (e.g., HIV) infections, brain trauma, including stroke, lead to long-term systemic immune suppression, resulting in higher infection and mortality rates. Further, hepatic invariant NKT cells have been shown to be important to ameliorate systemic immunosuppression. The present disclosure represents a strategy to prevent systemic immunosuppression and infections in these patients through modulation of NK, NKT and other immune cells.

[00258] In some cases, a method of the present disclosure of treating an immune suppression, stroke or brain trauma disorder comprises administering an immunomodulatory composition to an individual in need thereof, and further comprising administering to the individual an effective amount of at least one additional therapeutic agent.

Methods of enhancing the efficacy and/or reducing the toxicity of a therapeutic treatment

[00259] The present disclosure also provides methods for enhancing the efficacy and/or reducing the toxicity of a therapeutic treatment, and/or preventing the drug-resistance and

altering metabolism, preferably treatment with an anti-infective (such as antibacterial, antifungal or antiviral), anticancer agents, therapeutic antibodies, anti-inflammatory agents, metabolic disorder related drugs, immunostimulatory agents, immunomodulatory compounds, immunoregulatory agents, Si RNAs, therapeutic microbes including probiotics and microbiome (viable, inactivated, heat-killed, mutated, attenuated, genetically engineered) or a surgical treatment by administering an effective amount of an immunomodulatory composition of the present disclosure to an individual, cells or tissues preferably the amount needed to regulate an immune response.

[00260] In some cases, a method of the present disclosure of enhancing efficacy and reducing toxicity comprises administering an immunomodulatory composition to an individual in need thereof, and further comprising administering to the individual an effective amount of at least one additional therapeutic agent.

[00261] Non-limiting exmples of the suitable therapeutic agents and antibodies are described herein above in methods sections.

Methods of modulating dendritic cells

[00262] The present disclosure provides a method of modulating dendritic cells, the method comprising: a) contacting dendritic cells (DCs) obtained from an individual with a composition comprising: i) *Caulobacter crescentus*; and/or ii) an antigen. The DCs are contacted with the CC and the antigen is *in vitro*. Contacting DCs with the antigen and the CC modulates antigen presentation of the antigen on the DCs, thereby generating a population of modulated DCs. In some cases, the antigen can be contacted with DCs using methods such as diffusion, electroporation, active transport, liposome fusion, phagocytosis, sonication etc. In some cases, the method further comprises administering the antigen-presenting DCs to the individual from whom the DCs were obtained. In some cases, the method further comprises administering the antigen-presenting DCs combined with antibodies, chemotherapeutic agents, or cytokines to the individual from whom the DCs were obtained. Administering modulated DCs to an individual can treat a disease in the individual.

[00263] Suitable antigens are described above. In some cases, a composition comprising CC and antigen is contacted with DCs; and the CC-antigen-DC mixture is incubated for a period of time of from about 30 minutes to about 48 hours, thereby generating a population of antigen-presenting DCs. A subject method can modulate the proportion of DCs that are antigen-presenting DCs by at least about 25%, at least about 50%, at least about 75%, at least about 2-fold, at least about 5-fold, at least about 10-fold, at least about

25-fold, at least about 50-fold, at least about 100-fold, or more than 100-fold, compared to the proportion of DCs in the starting population that are antigen-presenting DCs.

Methods of generating regulatory immune cells

[00264] The present disclosure provides a method of generating regulatory lymphocytes such as NK, NKT, γδ T cells, ILCs, T cells, and B cells, the method comprising: a) contacting lymphocytes (NK, NKT, γδ T cells, ILCs, T cells, and/or B cells) obtained from an individual with a composition comprising: i) *Caulobacter crescentus*; and/or ii) an antigen in the presence or absence of antigen presenting cells. Contacting lymphocytes and the CC generates a population of regulatory lymphocytes. In some cases, the method comprises administering the regulatory lymphocytes to the individual from whom the cells were obtained, to prevent and/or treat a disease in a host. In some cases, the method further comprises administering the regulatory lymphocytes combined with antibodies, chemotherapeutic agents, or cytokines to the individual from whom the cells were obtained, to prevent and/or treat a disease in a host.

Methods of treating an infection with an intracellular pathogen

[00265] The present disclosure provides methods of preventing and/or treating infections with intracellular pathogens (e.g., viruses, mycobacteria, bacteria, parasites etc.) in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of the present disclosure.

[00266] In some cases, a method of the present disclosure of treating an intracellular pathogen comprises administering to an individual in need thereof, and further comprising administering to the individual an effective amount of at least one additional therapeutic agent.

Methods of modulating immune responses in animal models or cell culture for research, diagnosis and/or therapeutic purposes

[00267] The present disclosure provides a method of modulating immune responses in animal models for research purposes. The present disclosure further provides a method of modulating various TLRs, NLRs, DCs and/or effector lymphocytes such as NK, NKT, T and B cells, the method comprising: a) contacting effector cells (NK, NKT, T and B cells) obtained from an individual with a composition comprising: i) *Caulobacter crescentus*; and/or ii) an antigen in the presence or absence of antigen presenting cells. Contacting effector lymphocytes and the CC modulates their activation, thereby generating a population of regulated effector lymphocytes. In some cases, the method comprises of diagnosing a disease state by identifying and expanding specific antigen

reactive T cells and/or B cells. In some cases, the method comprises of identifying and expanding specific antigen reactive T cells and/or B cells in vitro for research purposes. In some cases the method comprises of administering the activated effector lymphocytes to the individual from whom the cells were obtained, to prevent and/or treat a disease in a host. In some cases, the method comprises of activating TLRs or NLRs for research and/or diagnostic purposes.

Methods of inducing proliferation, differentiation and/or modulation of stem cells

[00268] The present disclosure provides a method of inducing proliferation, differentiation and/or modulation of stem cells and restoration of homeostasis in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of the present disclosure. The present disclosure provides a method of modifying stem cells, the method comprising contacting the stem cells with a composition comprising *Caulobacter crescentus*, wherein said contacting generates a population of expanded, differentiated and/or modulated stem cells.

[00269] The present disclosure also provides a method of inducing proliferation, differentiation and/or moduation of stem cells, the method comprising contacting stem cells obtained from an individual with an immunomodulatory composition of the present disclosure, e.g., an immunomodulatory composition comprising *Caulobacter crescentus*. Contacting the stem cells with the CC leads to their proliferation and differentiation, thereby generating a population of expanded,differentiated and/or modulated cells. The population of expanded, differentiated and/or modulated cells can then be administered to the individual from whom the stem cells were obtained.

[00270] In some embodiments, a method of the present disclosure of inducing proliferation, differentiation and/or modulation of stem cells comprises: a) obtaining stem cells from an individual; b) contacting the stem cells *in vitro* with CC, thereby generating a population of expanded, differentiated and/or modulated cells; and c) administering the population of expanded, differentiated and/or modulated cells to the individual.

[00271] In some embodiments, a method of the present disclosure of inducing proliferation, differentiation and/or modulation of stem cells in an individual comprises administering to the individual an effective amount of an immunomodulatory composition of the present disclosure. In some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to induce proliferation, differentiation and/or modulation of hematpoietic stem cells, and restore homeostasis. For

example, in some cases, an effective amount of an immunomodulatory composition of the present disclosure is an amount that is effective, when administered in a single dose or in multiple doses, to induce proliferation, differentiation and/or modulation of hematpoietic stem cells, and restore homeostasis in an individual by 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 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 10-fold, more than 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 50-fold, at least 100-fold, or more than 100-fold, compared to the individual in the absence of treatment with the immunomodulatory composition.

Method of delivering therapeutic molecules

[00272] The present disclosure provides a method of delivering therapeutic molecules such as a protein, peptide, siRNA, carbohydrate, macromolecules etc. where *Caulobacter crescentus* can act as a carrier and/or delivery vehicle to deliver the therapeutic molecule. As a non genetic modification (GM), such as electrostatic and hydrophobic interactions, binding of molecules to the *Caulobacter crescentus* surface may enable the *Caulobacter crescentus* to act as a carrier and/or delivery vehicle. Further, due to bioadhesion/mucoadhesion, *Caulobacter crescentus* may facilitate uptake of the delivered by M cell transport at mucosal surfaces.

FORMULATIONS, DOSAGES, AND ROUTES OF ADMINISTRATION

[00273] An immunomodulatory composition of the present disclosure can include one or more pharmaceutically acceptable excipients; and can be formulated in any of a variety of ways, that may depend, e.g., on the route of administration. Pharmaceutically acceptable excipients are known to those skilled in the art, and have been amply described in a variety of publications, including, for example, A. Gennaro (1995) "Remington: The Science and Practice of Pharmacy", 19th edition, Lippincott, Williams, & Wilkins. Suitable excipient vehicles include, for example, water, saline, dextrose, glycerol, ethanol, inert proteins, hydrophillic polymers, amino acids, fatty acids, surfactants, non-ionic surfactants, carbohydrates, dextrins, polyols, chelating agents, or the like, and combinations thereof. In addition, if desired, the vehicle may contain minor amounts of auxiliary substances such as wetting or emulsifying agents or pH buffering agents. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in the art. See, e.g., Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 17th edition, 1985; Remington: The Science and Practice of Pharmacy, A.R. Gennaro, (2000) Lippincott, Williams & Wilkins.

[00274] An immunomodulatory composition can be incorporated into a variety of formulations for therapeutic administration. More particularly, an immunomodulatory composition can be formulated into pharmaceutical compositions by combination with appropriate, pharmaceutically acceptable carriers, salts, preservatives, buffering agents, or diluents, and may be formulated into preparations in solid, semi-solid, liquid, lyophilized, freeze-dried or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, skin patches, inhalants and aerosols. In other embodiments, the formulation comprises a colloidal delivery system that includes e.g., liposomes, nano-particles, nano-emulsions, nano capsules, microspheres and polymers.

[00275] In pharmaceutical dosage forms, an immunomodulatory composition may be administered alone or in appropriate association, as well as in combination, with other pharmaceutically active compounds. An immunomodulatory composition, an antigen, adjuvant and/or therapeutic drug can be administered concurrently, simultaneously, sequentially or at different times, at the same or different sites, and via different routes. The following methods and excipients are merely exemplary and are in no way limiting.

[00276] For oral preparations, an immunomodulatory composition can be used alone or in combination with appropriate additives to make tablets, powders, granules or capsules, for example, with conventional additives, such as lactose, mannitol, corn starch or potato starch; with binders, such as crystalline cellulose, cellulose derivatives, acacia, corn starch or gelatins; with disintegrators, such as corn starch, potato starch or sodium carboxymethylcellulose; with lubricants, such as talc or magnesium stearate; and if desired, with diluents, buffering agents, moistening agents, preservatives and flavoring agents.

[00277] An immunomodulatory composition can be formulated into liquid preparations for administration by dissolving, suspending or emulsifying the composition in an aqueous or nonaqueous solvent, such as vegetable or other similar oils, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol; and if desired, with conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives.

[00278] An immunomodulatory composition can be utilized in aerosol formulation to be administered via inhalation. The immunomodulatory compositions of the present disclosure can be formulated into pressurized acceptable propellants such as dichlorodifluoromethane, propane, nitrogen and the like.

[00279] Furthermore, an immunomodulatory composition can be made into suppositories by mixing with a variety of bases such as emulsifying bases or water-soluble bases. An immunomodulatory composition can be administered rectally via a suppository. The suppository can include vehicles such as cocoa butter, carbowaxes and polyethylene glycols, which melt at body temperature, yet are solidified at room temperature.

[00280] An immunomodulatory composition of the present disclosure can also be administered in the form of liposomes or liposomal polymeric gels. Liposomes can be given by a variety of routes, oral, nasal, parenteral, trans-dermal, inhalation etc. As is known in the art, liposomes are derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multilamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to an immunomodulatory composition of the present disclosure, one or more of a stabilizer, a preservative, an excipients, and the like. Exemplary lipids are the phospholipids and the phosphatidylcholines (lecithins), both natural and synthetic. Liposomes can be in a size range of from less than 100 nm to several microns. Methods to form liposomes are known in the art. for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

[00281] Unit dosage forms for oral or rectal administration such as syrups, elixirs, emulsions, and suspensions may be provided wherein each dosage unit, for example, teaspoonful, tablespoonful, tablet or suppository, contains a predetermined amount of the composition containing one or more active agents. Similarly, unit dosage forms for injection or intravenous administration may comprise an immunomodulatory composition as a solution in sterile water, normal saline or another pharmaceutically acceptable carrier.

[00282] A subject immunomodulatory composition can be formulated for topical administration. Topical administration includes administration to the skin or mucosa, including surfaces of the lung eye, nose, and ear. Suitable topical preparations include, e.g., skin patch preparation, transdermal patch preparation, micro arrays, cream, lotion, gel preparations, powder, ointment, paste, intranasal drops or gels.

[00283] Ointments are semi-solid preparations, which are typically based on petrolatum or other petroleum derivatives. Suitable ointments include oleaginous bases; emulsifiable bases; emulsion bases; and water-soluble bases. Oleaginous ointment bases include, for

example, vegetable oils, fats obtained from animals, and semisolid hydrocarbons obtained from petroleum. Emulsifiable ointment bases, also known as absorbent ointment bases, contain little or no water and include, for example, hydroxystearin sulfate, anhydrous lanolin and hydrophilic petrolatum. Emulsion ointment bases are either water-in-oil (WIO) emulsions or oil-in-water (OIW) emulsions, and include, for example, cetyl alcohol, glyceryl monostearate, lanolin and stearic acid. Exemplary water-soluble ointment bases are prepared from polyethylene glycols of varying molecular weight.

[00284] Lotions are preparations to be applied to the skin surface without friction, and are typically liquid or semi liquid preparations in which solid particles, including the active agent, are present in a water or alcohol base. Lotions are usually suspensions of solids, and preferably, for the present purpose, comprise a liquid oily emulsion of the oil-in-water type. Lotions can be used for treating large body areas, because of the ease of applying a more fluid composition. Lotions may contain suspending agents to produce better dispersions as well as compounds useful for localizing and holding the active agent in contact with the skin, e.g., methyl cellulose, sodium carboxymethyl-cellulose, or the like. An example of a lotion formulation for use in conjunction with the present invention contains propylene glycol mixed with a hydrophilic petrolatum such as that which may be obtained under the trademark Aquaphor® from Beiersdorf, Inc. (Norwalk, Coon.).

[00285] Suitable creams can be viscous liquid or semisolid emulsions, either oil-in-water or water-in-oil. Cream bases are water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also sometimes called the "internal" phase, is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol; the aqueous phase usually, although not necessarily, exceeds the oil so phase in volume, and generally contains a humectant. The emulsifier in a cream formulation, as explained in Remington, supra, is generally a nonionic, anionic, cationic or amphoteric surfactant.

[00286] Gels formulations can be used. Gels are semisolid, suspension-/type systems. Single-phase gels contain organic macromolecules distributed substantially uniformly throughout the carrier liquid, which can be aqueous, but may also contain an alcohol and, optionally, an oil.

[00287] A topical formulation may also be delivered to the skin using conventional "transdermal"-type patches, wherein the agent (immunomodulatory composition) is contained within a laminated structure that serves as a delivery device to be affixed to the skin. In such a structure, the immunomodulatory composition is contained in a layer, or "reservoir," underlying an upper backing layer. The laminated structure may contain a

single reservoir, or it may contain multiple reservoirs. In one embodiment, the reservoir comprises a polymeric matrix of a pharmaceutically acceptable contact adhesive material that serves to affix the system to the skin during drug delivery. Examples of suitable skin contact adhesive materials include, but are not limited to, polyethylenes, polysioxanes, polyisobutylenes, polyacrylates, polyurethanes, and the like. The particular polymeric adhesive selected will depend on the particular immunomodulatory composition, vehicle, etc., i.e., the adhesive must be compatible with all components of the drug-containing composition. In an alternative embodiment, the immunomodulatory composition-containing reservoir and skin contact adhesive are present as separate and distinct layers, with the adhesive underlying the reservoir which, in this case, may be either a polymeric matrix as described above, or it may be a liquid or hydrogel reservoir, or may take some other form.

[00288] The term "unit dosage form," as used herein, refers to physically discrete units suitable as unitary dosages for human and animal subjects, each unit containing a predetermined quantity of an active agent (e.g., CC; antigen; etc.) calculated in an amount sufficient to produce the desired effect in association with a pharmaceutically acceptable diluent, carrier or vehicle. The specifications for the active agents depend on the particular compound employed and the effect to be achieved, and the pharmacodynamics associated with each compound in the host.

[00289] Other modes of administration will also find use. For instance, an immunomodulatory composition can be formulated in suppositories and, in some cases, aerosol and intranasal compositions. For suppositories, the vehicle composition will include traditional binders and carriers such as, polyalkylene glycols, or triglycerides. Such suppositories may be formed from mixtures containing the active ingredient in the range of about 0.5% to about 10% (w/w), or about 1% to about 2%.

[00290] Intranasal formulations will usually include vehicles that neither cause irritation to the nasal mucosa nor significantly disturb ciliary function. Diluents such as water, aqueous saline or other known substances can be employed. The nasal formulations may also contain preservatives such as, but not limited to, chlorobutanol and benzalkonium chloride. A surfactant may be present to enhance absorption of the subject proteins by the nasal mucosa.

[00291] An immunomodulatory composition can be administered as injectables. Typically, injectable compositions are prepared as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection may also

be prepared. The preparation may also be emulsified or the active ingredient encapsulated in liposome vehicles.

[00292] Suitable excipient vehicles are, for example, water, saline, dextrose, glycerol, ethanol, or the like, and combinations thereof. In addition, if desired, the vehicle may contain minor amounts of auxiliary substances such as wetting or emulsifying agents or pH buffering agents. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in the art. See, e.g., Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 17th edition, 1985; Remington: The Science and Practice of Pharmacy, A.R. Gennaro, (2000) Lippincott, Williams & Wilkins. The composition or formulation to be administered will, in any event, contain a quantity of an active agent (e.g., CC; antigen; etc.) adequate to achieve the desired state in the subject being treated.

[00293] The pharmaceutically acceptable excipients, such as vehicles, adjuvants, salts, carriers or diluents, are readily available to the public. Moreover, pharmaceutically acceptable auxiliary substances, such as pH adjusting and buffering agents, tonicity adjusting agents, stabilizers, emulsifying agents, surfactants, preservatives, amino acids, fatty acids, wetting agents and the like, are readily available to the public.

Oral Formulations

[00294] In some embodiments, an immunomodulatory composition is formulated for oral delivery to an individual in need of such an immunomodulatory composition.

[00295] For oral delivery, a subject formulation comprising an immunomodulatory composition will in some embodiments include an enteric-soluble coating material. Suitable enteric-soluble coating material include hydroxypropyl methylcellulose acetate succinate (HPMCAS), hydroxypropyl methyl cellulose phthalate (HPMCP), cellulose acetate phthalate (CAP), polyvinyl phthalic acetate (PVPA), Eudragit™, and shellac.

[00296] Suitable oral formulations also include an immunomodulatory composition, formulated with any of the following: microgranules (see, e.g., U.S. Patent No. 6,458,398); biodegradable macromers (see, e.g., U.S. Patent No. 6,703,037); biodegradable hydrogels (see, e.g., Graham and McNeill (1989) *Biomaterials* 5:27-36); biodegradable particulate vectors (see, e.g., U.S. Patent No. 5,736,371); bioabsorbable lactone polymers (see, e.g., U.S. Patent No. 5,631,015); slow release protein polymers (see, e.g., U.S. Patent No. 6,699,504; Pelias Technologies, Inc.); a poly(lactide-co-glycolide/polyethylene glycol block copolymer (see, e.g., U.S. Patent No. 6,630,155; Atrix Laboratories, Inc.); a composition comprising a biocompatible polymer and

particles of metal cation-stabilized agent dispersed within the polymer (see, e.g., U.S. Patent No. 6,379,701; Alkermes Controlled Therapeutics, Inc.); and microspheres (see, e.g., U.S. Patent No. 6,303,148; Octoplus, B.V.).

[00297] Suitable oral formulations also include an immunomodulatory composition formulated with any of the following: a carrier such as Emisphere® (Emisphere Technologies, Inc.); TIMERx, a hydrophilic matrix combining xanthan and locust bean gums which, in the presence of dextrose, form a strong binder gel in water (Penwest); Geminex™ (Penwest); Procise™ (GlaxoSmithKline); SAVIT™ (Mistral Pharma Inc.); RingCap™ (Alza Corp.); Smartrix® (Smartrix Technologies, Inc.); SQZgel™ (MacroMed, Inc.); Geomatrix™ (Skye Pharma, Inc.); Oros® Tri-layer (Alza Corporation); and the like.

[00298] Also suitable for use are formulations such as those described in U.S. Patent No. 6,296,842 (Alkermes Controlled Therapeutics, Inc.); U.S. Patent No. 6,187,330 (Scios, Inc.); and the like.

[00299] Also suitable for use herein are formulations comprising an intestinal absorption enhancing agent. Suitable intestinal absorption enhancers include, but are not limited to, calcium chelators (e.g., citrate, ethylenediamine tetracetic acid); surfactants (e.g., sodium dodecyl sulfate, bile salts, palmitoylcarnitine, and sodium salts of fatty acids); toxins (e.g., zonula occludens toxin); and the like.

[00300] Suitable oral formulations also include an immunomodulatory composition, formulated as a food supplement (e.g. nutraceuticals, yogurt, frozen yogurt, milk powder, cheese, bars, drinks, prebiotics, symbiotics, paraprobiotics) etc.

Controlled release formulations

[00301] In some embodiments, an immunomodulatory composition is formulated in a controlled release formulation.

[00302] Controlled release can be taken to mean any one of a number of extended release dosage forms. The following terms may be considered to be substantially equivalent to controlled release, for the purposes of the present invention: continuous release, controlled release, delayed release, depot, gradual release, long-term release, programmed release, prolonged release, proportionate release, protracted release, repository, retard, slow release, spaced release, sustained release, time coat, timed release, delayed action, extended action, layered-time action, long acting, prolonged action, repeated action, slowing acting, sustained action, sustained-action medications,

and extended release. Further discussions of these terms may be found in Lesczek Krowczynski, Extended-Release Dosage Forms, 1987 (CRC Press, Inc.).

[00303] The various controlled release technologies cover a very broad spectrum of drug dosage forms. Controlled release technologies include, but are not limited to physical systems and chemical systems.

[00304] Physical systems include, but are not limited to, reservoir systems with rate-controlling membranes, such as microencapsulation, macroencapsulation, and membrane systems; reservoir systems without rate-controlling membranes, such as hollow fibers, ultra microporous cellulose triacetate, and porous polymeric substrates and foams; monolithic systems, including those systems physically dissolved in non-porous, polymeric, or elastomeric matrices (e.g., nonerodible, erodible, environmental agent ingression, and degradable), and materials physically dispersed in non-porous, polymeric, or elastomeric matrices (e.g., nonerodible, erodible, environmental agent ingression, and degradable); laminated structures, including reservoir layers chemically similar or dissimilar to outer control layers; and other physical methods, such as osmotic pumps, or adsorption onto ion-exchange resins.

[00305] Chemical systems include, but are not limited to, chemical erosion of polymer matrices (e.g., heterogeneous, or homogeneous erosion), or biological erosion of a polymer matrix (e.g., heterogeneous, or homogeneous). Additional discussion of categories of systems for controlled release may be found in Agis F. Kydonieus, Controlled Release Technologies: Methods, Theory and Applications, 1980 (CRC Press, Inc.).

[00306] There are a number of controlled release drug formulations that are developed for oral administration. These include, but are not limited to, osmotic pressure-controlled gastrointestinal delivery systems; hydrodynamic pressure-controlled gastrointestinal delivery systems; membrane permeation-controlled gastrointestinal delivery systems, which include microporous membrane permeation-controlled gastrointestinal delivery devices; gastric fluid-resistant intestine targeted controlled-release gastrointestinal delivery devices; gel diffusion-controlled gastrointestinal delivery systems; and ion-exchange-controlled gastrointestinal delivery systems, which include cationic and anionic drugs. Additional information regarding controlled release drug delivery systems may be found in Yie W. Chien, Novel Drug Delivery Systems, 1992 (Marcel Dekker, Inc.). Some of these formulations will now be discussed in more detail.

[00307] Enteric coatings are applied to tablets to prevent the release of active agents in the stomach either to reduce the risk of unpleasant side effects or to maintain the stability of the drug which might otherwise be subject to degradation of expose to the gastric environment. Most polymers that are used for this purpose are polyacids that function by virtue or the fact that their solubility in aqueous medium is pH-dependent, and they require conditions with a pH higher than normally encountered in the stomach.

[00308] One exemplary type of oral controlled release structure is enteric coating of a solid or liquid dosage form. The enteric coatings are designed to disintegrate in intestinal fluid for ready absorption. Delay of absorption of the active agent that is incorporated into a formulation with an enteric coating is dependent on the rate of transfer through the gastrointestinal tract, and so the rate of gastric emptying is an important factor. Some investigators have reported that a multiple-unit type dosage form, such as granules, may be superior to a single-unit type.

[00309] Suitable enteric coating agents include, but are not limited to, hydroxypropylmethylcellulose phthalate, methacryclic acid-methacrylic acid ester copolymer, polyvinyl acetate-phthalate and cellulose acetate phthalate.

[00310] Another type of useful oral controlled release structure is a solid dispersion. A solid dispersion may be defined as a dispersion of one or more active ingredients in an inert carrier or matrix in the solid state prepared by the melting (fusion), solvent, or melting-solvent method.

[00311] Examples of carriers useful in solid dispersions include, but are not limited to, water-soluble polymers such as polyethylene glycol, polyvinylpyraolidone, and hydroxypropylmethylcellulose. Alternative carriers include phosphatidylcholine. Phosphatidylcholine is an amphoteric but water-insoluble lipid, which may improve the solubility of otherwise insoluble active agents in an amorphous state in phosphatidylcholine solid dispersions.

[00312] Other carriers include polyoxyethylene hydrogenated castor oil. An immunomodulatory composition can be included in a solid dispersion system with an enteric polymer such as hydroxypropylmethylcellulose phthalate and carboxymethylethylcellulose, and a non-enteric polymer, hydroxypropylmethylcellulose. Another solid dispersion dosage form includes incorporation of the drug of interest (e.g., an active agent) with ethyl cellulose and stearic acid in different ratios.

[00313] There are various methods commonly known for preparing solid dispersions. These include, but are not limited to, the melting method, the solvent method and the melting-solvent method.

[00314] Injectable microspheres are another controlled release dosage form. Injectable micro spheres may be prepared by non-aqueous phase separation techniques, and spray-drying techniques. Microspheres may be prepared using polylactic acid or copoly(lactic/glycolic acid).

[00315] Other controlled release technologies that may be used include, but are not limited to, SODAS (Spheroidal Oral Drug Absorption System), INDAS (Insoluble Drug Absorption System), IPDAS (Intestinal Protective Drug Absorption System), MODAS (Multiporous Oral Drug Absorption System), EFVAS (Effervescent Drug Absorption System), PRODAS (Programmable Oral Drug Absorption System), and DUREDAS (Dual Release Drug Absorption System) available from Elan Pharmaceutical Technologies. SODAS are multi particulate dosage forms utilizing controlled release beads. INDAS are a family of drug delivery technologies designed to increase the solubility of poorly soluble drugs. IPDAS are multi particulate tablet formation utilizing a combination of high density controlled release beads and an immediate release granulate. MODAS are controlled release single unit dosage forms. Each tablet consists of an inner core surrounded by a semipermeable multiparous membrane that controls the rate of drug release. EFVAS is an effervescent drug absorption system. PRODAS is a family of multi particulate formulations utilizing combinations of immediate release and controlled release mini-tablets. DUREDAS is a bilayer tablet formulation providing dual release rates within the one dosage form. Although these dosage forms are known to one of skill, certain of these dosage forms will now be discussed in more detail.

[00316] An immunomodulatory composition of the present disclosure can be incorporated into any one of the aforementioned controlled released dosage forms, or other conventional dosage forms. The amount of active agent contained in each dose can be adjusted, to meet the needs of the individual patient, and the indication. One of skill in the art and reading this disclosure will readily recognize how to adjust the level of an active agent and the release rates in a controlled release formulation, in order to optimize delivery of an active agent and its bioavailability.

Inhalational formulations

[00317] An immunomodulatory composition of the present disclosure will in some embodiments be administered to a patient by means of a pharmaceutical delivery system

for the inhalation route. The immunomodulatory composition may be formulated in a form suitable for administration by inhalation. The inhalational route of administration provides the advantage that the inhaled drug can bypass the blood-brain barrier. The pharmaceutical delivery system is one that is suitable for respiratory therapy by delivery of an active agent to mucosal linings of the bronchi. A system that depends on the power of a compressed gas to expel the immunomodulatory composition from a container can also be used. An aerosol or pressurized package can be employed for this purpose.

[00318] As used herein, the term "aerosol" is used in its conventional sense as referring to very fine liquid or solid particles carries by a propellant gas under pressure to a site of therapeutic application. When a pharmaceutical aerosol is employed, the aerosol contains the therapeutically active compound (e.g., active agent), which can be dissolved, suspended, or emulsified in a mixture of a fluid carrier and a propellant. The aerosol can be in the form of a solution, suspension, emulsion, powder, or semi-solid preparation. Aerosols can be used for administration as fine, solid particles or as liquid mists via the respiratory tract of a patient. Various types of propellants known to one of skill in the art can be utilized. Suitable propellants include, but are not limited to, hydrocarbons or other suitable gas. In the case of the pressurized aerosol, the dosage unit may be determined by providing a value to deliver a metered amount.

[00319] An immunomodulatory composition can also be formulated for delivery with a nebulizer, which is an instrument that generates very fine liquid particles of substantially uniform size in a gas. For example, a liquid containing the immunomodulatory composition is dispersed as droplets. The small droplets can be carried by a current of air through an outlet tube of the nebulizer. The resulting mist penetrates into the respiratory tract of the patient.

[00320] There are several different types of inhalation methodologies which can be employed in connection with an immunomodulatory composition of the present disclosure. An immunomodulatory composition can be formulated with low boiling point propellants. Such formulations are generally administered by conventional meter dose inhalers (MDI's). Alternatively, immunomodulatory composition can be formulated in aqueous or ethanolic solutions and delivered by conventional nebulizers. In some embodiments, such solution formulations are aerosolized using devices and systems such as disclosed within U.S. Patent 5,497,763; 5,544,646; 5,718,222; and 5,660,166. An immunomodulatory composition can be formulated into dry powder formulations. Such formulations can be administered by simply inhaling the dry powder formulation after

creating an aerosol mist of the powder. Technology for carrying such out is described within U.S. Patent 5,775,320 issued July 7, 1998 and U.S. Patent 5,740,794 issued April 21, 1998.

[00321] An immunomodulatory composition of the present disclosure will in some embodiments be formulated for vaginal delivery. A subject immunomodulatory composition for intravaginal administration can be formulated as an intravaginal bioadhesive tablet, intravaginal bioadhesive microparticle, intravaginal cream, intravaginal lotion, intravaginal foam, intravaginal ointment, intravaginal paste, intravaginal solution, or intravaginal gel.

[00322] A subject immunomodulatory composition will in some embodiments be formulated for rectal delivery. A subject formulation for intrarectal administration comprises a subject immunomodulatory composition formulated as an intrarectal bioadhesive tablet, intrarectal bioadhesive microparticle, intrarectal cream, intrarectal lotion, intrarectal foam, intrarectal ointment, intrarectal paste, intrarectal solution, or intrarectal gel. An immunomodulatory composition of the present disclosure can be formulated with agents that improve adhesion to mucosal membranes such as mucoadhesives, bioadhesives, particles, microspheres or liposomes.

[00323] A subject immunomodulatory composition can include one or more of an excipient (e.g., sucrose, starch, mannitol, sorbitol, lactose, glucose, cellulose, talc, calcium phosphate or calcium carbonate), a binder (e.g., cellulose, methylcellulose, hydroxymethylcellulose, polypropylpyrrolidone, polyvinylpyrrolidone, gelatin, gum arabic, poly(ethylene glycol), sucrose or starch), a disintegrator (e.g., starch, carboxymethylcellulose, hydroxypropyl starch, low substituted hydroxypropylcellulose, sodium bicarbonate, calcium phosphate or calcium citrate), a lubricant (e.g., magnesium stearate, light anhydrous silicic acid, talc or sodium lauryl sulfate), a flavoring agent (e.g., citric acid, menthol, glycine or orange powder), a preservative (e.g., sodium benzoate, sodium bisulfite, methylparaben or propylparaben), a stabilizer (e.g., citric acid, sodium citrate or acetic acid), a suspending agent (e.g., methylcellulose, polyvinylpyrrolidone or aluminum stearate), a dispersing agent (e.g., hydroxypropylmethylcellulose), a diluent (e.g., water), and base wax (e.g., cocoa butter, white petrolatum or polyethylene glycol).

[00324] Tablets comprising an immunomodulatory composition may be coated with a suitable film-forming agent, e.g., hydroxypropylmethyl cellulose, hydroxypropyl cellulose or ethyl cellulose, to which a suitable excipient may optionally be added, e.g., a softener such as glycerol, propylene glycol, diethylphthalate, or glycerol triacetate; a

filler such as sucrose, sorbitol, xylitol, glucose, or lactose; a colorant such as titanium hydroxide; and the like.

Dosages

[00325] The dosage of an immunomodulatory composition of the present disclosure can vary, depending on factors such as the clinical goals to be achieved, the age of the individual being treated, the physical status of the individual being treated, etc.

[00326] An immunomodulatory composition of the present disclosure can comprise CC in an amount of from about 10^3 CC per unit dosage form to about 10^{20} CC per unit dosage form. For example, an immunomodulatory composition of the present disclosure can comprise CC in an amount of from about 10^3 CC per unit dosage form to about 10^4 CC per unit dosage form, from about 10^4 CC per unit dosage form to about 10^5 CC per unit dosage form, from about 10^5 CC per unit dosage form to about 10^6 CC per unit dosage form, from about 10^6 CC per unit dosage form to about 10^7 CC per ml, from about 10^8 CC per unit dosage form to about 10^9 CC per unit dosage form, from about 10^9 CC per ml to about 10^{10} CC per unit dosage form, from about 10^{15} CC per unit dosage form to about 10^{20} CC per unit dosage form, or more than 10^{20} CC per unit dosage form.

[00327] For example, an immunomodulatory composition of the present disclosure can comprise CC in an amount of from about 10^3 CC per ml to about 10^{20} CC per ml. For example, an immunomodulatory composition of the present disclosure can comprise CC in an amount of from about 10^3 CC per ml to about 10^4 CC per ml, from about 10^4 CC per ml to about 10^5 CC per ml, from about 10^5 CC per ml to about 10^6 CC per ml, from about 10^6 CC per ml to about 10^7 CC per ml, from about 10^8 CC per ml to about 10^9 CC per ml, from about 10^9 CC per ml to about 10^{10} CC per ml, from about 10^{15} CC per ml to about 10^{20} CC per ml, or more than 10^{20} CC per ml.

[00328] An immunomodulatory composition of the present disclosure can comprise CC in an amount of from about 10^2 to about 10^{20} colony forming units (cfu) per unit dosage form; for example, an immunomodulatory composition of the present disclosure can comprise CC in an amount of from about 10^2 to about 10^3 from about 10^3 to about 10^5, from about 10^5 to about 10^7, from about 10^7 to about 10^9, from about 10^9 to about 10^{11}, from about 10^{11} to about 10^{13}, from about 10^{13} to about 10^{15}, from about 10^{15} to about 10^{18}, or from about 10^{18} to about 10^{20}, cfu per unit dosage form. A unit dosage form can be an amount that is administered in a single dose; for example, a unit dosage form can be 0.5 ml, 1.0 ml, or other volume suitable for administration in a single dose.

[00329] An immunomodulatory composition of the present disclosure can comprise CC in an amount of from about 10^3 CC per mg to about 10^{12} CC per mg. For example, an immunomodulatory composition of the present disclosure can comprise CC in an amount of from about 10^3 CC per mg to about 10^4 CC per mg, from about 10^4 CC per mg to about 10^5 CC per mg, from about 10^5 CC per mg to about 10^6 CC per mg, from about 10^6 CC per mg to about 10^7 CC per mg, from about 10^8 CC per mg to about 10^9 CC per mg, from about 10^9 CC per mg to about 10^{10} CC per mg, from about 10^{10} CC per mg to about 10^{11} CC per mg, or from about 10^{11} CC per mg to about 10^{12} CC per mg.

[00330] An immunomodulatory composition of the present disclosure can comprise CC in an amount of from about 10^3 CC per gram to about 10^{15} CC per gram. For example, an immunomodulatory composition of the present disclosure can comprise CC in an amount of from about 10^3 CC per gram to about 10^4 CC per gram, from about 10^4 CC per gram to about 10^5 CC per gram, from about 10^5 CC per gram to about 10^6 CC per gram, from about 10^6 CC per gram to about 10^7 CC per gram, from about 10^8 CC per gram to about 10^9 CC per gram, from about 10^9 CC per gram to about 10^{10} CC per gram, from about 10^{10} CC per gram to about 10^{11} CC per gram, from about 10^{11} CC per gram to about 10^{12} CC per gram, from about 10^{12} CC per gram to about 10^{13} CC per gram, from about 10^{13} CC per gram to about 10^{14} CC per gram, or from about 10^{14} CC per gram to about 10^{15} CC per gram.

[00331] An immunomodulatory composition of the present disclosure can comprise CC in an amount of from about 10^2 to about 10^{20} cfu per ml; for example, an immunomodulatory composition of the present disclosure can comprise CC in an amount of from about 10^2 to about 10^3 from about 10^3 to about 10^5, from about 10^5 to about 10^7, from about 10^7 to about 10^9, from about 10^9 to about 10^{11}, from about 10^{11} to about 10^{13}, from about 10^{13} to about 10^{15}, from about 10^{15} to about 10^{18}, or from about 10^{18} to about 10^{20}, cfu per ml.

[00332] In some embodiments, multiple doses of an immunomodulatory composition of the present disclosure are administered. The frequency of administration of an immunomodulatory composition of the present disclosure can vary depending on any of a variety of factors, e.g., severity of the symptoms, etc. For example, in some embodiments, an immunomodulatory composition of the present disclosure is administered once per month, twice per month, three times per month, every other week (qow), once per week (qw), twice per week (biw), three times per week (tiw), four times

per week, five times per week, six times per week, every other day (qod), daily (qd), twice a day (qid), or three times a day (tid).

[00333] The duration of administration of an immunomodulatory composition of the present disclosure, e.g., the period of time over which an immunomodulatory composition of the present disclosure is administered, can vary, depending on any of a variety of factors, e.g., patient response, etc. For example, an immunomodulatory composition of the present disclosure can be administered over a period of time ranging from about one hour to one day, from about one day to about one week, from about two weeks to about four weeks, from about one month to about two months, from about two months to about four months, from about four months to about six months, from about six months to about eight months, from about eight months to about 1 year, from about 1 year to about 2 years, or from about 2 years to about 4 years, or more.

[00334] Where an immunomodulatory composition comprises an antigen, the dosage of antigen is selected as an amount which is effective and modulates an immune response without significant adverse side effects. Such amount can vary, depending, e.g., upon which specific antigen is employed, the route of administration, etc. Where an immunomodulatory composition comprises an antigen, the dosage of antigen can range from 1 ng per unit dosage form to about 100 mg per unit dosage form, e.g., from about 1 ng to about 25 ng, from about 25 ng to about 50 ng, from about 50 ng to about 100 ng, from about 100 ng to about 250 ng, from about 250 ng to about 500 ng, from about 500 ng to about 750 ng, from about 750 ng to about 1 μg, from about 1 μg to about 25 μg, from about 25 μg to about 50 μg, from about 50 μg to about 100 μg, from about 100 μg to about 250 μg, from about 250 μg to about 500 μg, from about 500 μg to about 750 μg, from about 750 μg to about 1 mg, from about 1 mg to about 25 mg, from about 25 mg to about 50 mg, or from about 50 mg to about 100 mg, per unit dosage form.

Routes of administration

[00335] An immunomodulatory composition of the present disclosure is administered to an individual using any available method and route suitable for drug delivery, including *in vivo* and *ex vivo* methods, as well as systemic and localized routes of administration.

[00336] Conventional and pharmaceutically acceptable routes of administration include intranasal, intramuscular, intratracheal, subcutaneous, intradermal, intranodal, percutaneous, transdermal, intratumoral, topical application, intravenous, intravesicular, rectal, nasal, oral and other enteral and parenteral routes of administration. Routes of administration may be combined, if desired, or adjusted depending upon the agent and/or

the desired effect. The composition can be administered in a single dose or in multiple doses.

[00337] An immunomodulatory composition of the present disclosure can be administered to a host using any available conventional methods and routes suitable for delivery of conventional drugs, including systemic or localized routes. In general, routes of administration contemplated include, but are not necessarily limited to, enteral, parenteral, or inhalational routes.

[00338] Parenteral routes of administration other than inhalation administration include, but are not necessarily limited to, topical, transdermal, subcutaneous, intramuscular, intradermal, intralymphatic, intraorbital, intracapsular, intraspinal, intrasternal, intracranial, intravesicular, and intravenous routes, *i.e.*, any route of administration other than through the alimentary canal. Parenteral administration can be carried to effect systemic or local delivery of the immunomodulatory composition. Where systemic delivery is desired, administration typically involves invasive or systemically absorbed topical or mucosal administration of pharmaceutical preparations.

[00339] An immunomodulatory composition of the present disclosure can also be delivered to the subject by enteral administration. Enteral routes of administration include, but are not necessarily limited to, oral and rectal (*e.g.*, using a suppository) delivery.

[00340] An immunomodulatory composition of the present disclosure can also be delivered to the subject via a mucosal route of delivery. Mucosal routes of delivery include nasal, buccal, sublingual, vaginal, ocular, and rectal routes of administration.

[00341] In certain embodiments, an immunomodulatory composition of the present disclosure is administered to a subject via a combination of different routes in the order indicated below:

i. systemic, mucosal;

ii. systemic, systemic, mucosal, mucosal;

iii. systemic, mucosal, systemic;

iv. mucosal, mucosal, systemic, systemic;

v. mucosal, systemic, systemic;

vi. mucosal, systemic, mucosal, for example.

[00342] When an immunomodulatory composition of the present disclosure is administered systemically or mucosally more than once, the two or more systemic or mucosal administrations may be by the same systemic (for example, two intramuscular

injections) or mucosal route (two IN/SL administrations) or different (for example, one intramuscular injection and one intravenous injection; one IN administration and one SL administration).

[00343] An immunomodulatory composition of the present disclosure is administered to an individual using any available method, delivery or device such as vaccine patches, needles, microneedles (hollow or solid), drop, syrup, tablets, capsules, pipette, dose-spray pumps, nasal dropper, inhalation devices, liquid or dry powder, suspensions or solutions, spray devices, Accuspray™, thermoresponsive gels, jet injectors, Nasovak™, Bespak™, ointment, lotions, suppositories, gels etc.

[00344] Suitable routes of administration are known in the art; any known route of administration can be employed in connection with administering an immunomodulatory composition of the present disclosure. See, e.g., Nursing Drug Guide: Nursing Drug Handbook (2015) 36th ed, Lippincott.

INDIVIDUALS SUITABLE FOR TREATMENT

[00345] Individuals suitable for treatment using a method of the present disclosure include humans; non-human mammals; fish; and birds. In any of the above embodiments discussed below, the individual being treated using a subject method can be a non-human mammal such as livestock (e.g., pigs, sheep, goats, cattles, equine, caprine, ovine, bovine, etc.); a mammalian pet (e.g., cats; dogs; horses; etc.); a bird such as chicken, hens, turkeys, geese, quail, ducks etc.; or other animals such as fish.

[00346] In any of the above embodiments discussed below, the individual being treated using a subject method is a human of from about one month to about 6 months, from about 6 months to about 1 year, or from about 1 year to about 5 years of age. In any of the above embodiments discussed below, the individual being treated using a subject method is a human of from about 5 years to about 12 years, from about 13 years to about 18 years, or from about 18 years to about 25 years of age. In any of the above embodiments discussed below, the individual being treated using a subject method is a human of from about 25 years to about 50 years, from about 50 years to about 75 years of age, or older than 75 years of age. In any of the above embodiments discussed below, the individual being treated using a subject method is a human who is immunocompromised.

[00347] In some embodiments, the individual has a viral disease, or is at risk of contracting a viral disease. In some cases, the disease is a viral disease selected from the group consisting of, but not limited to, viral disease caused by Zika virus, hepatitis B, hepatitis C, rotavirus, human immunodeficiency virus, human T-cell lymphotropic virus,

DNA viruses such as parvoviruses, adeno viruses, papovaviruses (e.g., papilloma virus, polyoma viruses, and SV40), herpes viruses (e.g., herpes simplex type I (HSV-I), herpes simplex type II (HSV-II), and Epstein-Barr virus), poxviruses (e.g., variola (smallpox) and vaccinia virus); and RNA viruses, such as retroviruses [e.g. human immunodeficiency virus type I (HIV-I), human immunodeficiency virus type II (HIV-II), human T-cell lymphotropic virus type I (HTLV-I), human T-cell lymphotropic virus type II (HTLV-II)], orthomyxoviruses (e.g., influenza viruses), paramyxoviruses (e.g., measles virus, mumps virus, respiratory syncytial virus), rhabdoviruses (e.g., rabies virus), Sendai virus, picornaviruses (e.g., poliomyelitis virus, coxsackieviruses, rhinoviruses), reoviruses (e.g., rotavirus, colorado tick fever virus), togaviruses (e.g., rubella virus (German measles), Japanese encephalitis virus and Semliki forest virus), arboviruses, calciviruses (e.g., hepatitis E virus), flaviviruses (e.g., yellow fever virus, dengue virus), coronaviruses, filoviruses (e.g., Ebola and Marburg viruses) and Bunyaviruses (e.g., Hanta virus, California encephalitis virus).

[00348] In some embodiments, the individual has a bacterial infection, or is a risk of contracting a bacterial infection. In some embodiments, the individual has a mycobacterial infection, or is at risk of contracting a mycobacterial infection. In some embodiments, the individual is infected with, or is at risk of becoming infected with, a pathogenic bacterium. Pathogenic bacteria include, e.g., Gram positive bacteria, Gram negative bacteria, mycobacteria, etc. Non-limiting examples of pathogenic bacteria include Mycobacteria (e.g., *M. tuberculosis*, *M. avium* complex), nontuberculosis *Mycobacteria*, Streptococcus, Staphylococcus, Pseudomonas, Salmonella, Neisseria, and Listeria. In some cases, the bacteria is *Neisseria gonorrhea*, *M. tuberculosis*, *M. leprae*, *Listeria monocytogenes*, *Streptococcus pneumoniae*, *S. pyogenes*, *S. agalactiae*, *S. viridans*, *S. faecalis*, or *S. bovis*. Other examples of pathogenic bacteria contemplated include, but are not limited to, Gram positive bacteria (e.g., Listeria, Bacillus such as *Bacillus anthracis*, Erysipelothrix species), Gram negative bacteria (e.g., Bartonella, Brucella, Campylobacter, Enterobacter, Escherichia, Francisella, Hemophilus, Klebsiella, Morganella, Proteus, Providencia, Pseudomonas, Salmonella, Serratia, Shigella, Vibrio, and Yersinia species), spirochete bacteria (e.g., Borrelia species including Borrelia burgdorferi that causes Lyme disease), anaerobic bacteria (e.g., Actinomyces and Clostridium species), Gram positive and negative coccal bacteria, Enterococcus species, Streptococcus species, Pneumococcus species, Staphylococcus species, Neisseria species.

[00349] In some cases, the individual has, or is at risk of contracting, a parasitic disease. Parasitic diseases that can be treated or prevented by the methods of the present disclosure include, but are not limited to, amebiasis, malaria, leishmania, coccidia, giardiasis, cryptosporidiosis, toxoplasmosis, trypanosomiasis, schistosomiasis, and filariasis.

[00350] In some cases, the individual has, or is at risk of contracting, a fungal disease. Fungal diseases that can be treated or prevented by the methods of the present disclosure include, but are not limited to Candida spp. including *C. albicans*, Aspergillus spp., Cryptococcus spp. including *C. neoformans*, Blastomyces sp., Pneumocytes spp., yeast, mold, or Coccidioides spp.

[00351] In some cases, the individual has, or is at risk of contracting, a worm infection, a fluke infection, etc. Also encompassed are infections by various worms, such as but not limited to ascariasis, ancylostomiasis, trichuriasis, strongyloidiasis, toxoccariasis, trichinosis, onchocerciasis filaria, and dirofilariasis. Also encompassed are infections by various flukes, such as but not limited to schistosomiasis, paragonimiasis, and clonorchiasis.

[00352] In some embodiments, the individual has an autoimmune disorder, inflammatory disorder or an immune dysfunction, or is at risk of developing an autoimmune disorder, inflammatory disorder or an immune dysfunction. In some cases, the disease is selected from the group consisting of, but not limited to, allergy, rheumatoid arthritis, asthma, diabetes, systemic lupus erythematosus (SLE), Grave's disease, atherosclerosis, multiple sclerosis, schizophrenia, Alzheimer's, depression, hypopituitarism, neurodegenerative disorders, cardiovascular diseases, obesity, organ transplantation, sepsis, hepatic diseases, psoriasis, metabolic diseases, etc.

[00353] In some cases, the disease is selected from the group consisting of autoimmune and autoimmune-related diseases, including, but not limited to, acute disseminated encephalomyelitis, acute necrotizing hemorrhagic leukoencephalitis, Addison's disease, agammaglobulinemia, alopecia areata, amyloidosis, ankylosing spondylitis, anti-GBM/anti-TBM nephritis, antiphospholipid syndrome, angioedema, aplastic anemia, dysautonomia, hepatitis, hyperlipidemia, immunodeficiency, inner ear disease, myocarditis, oophoritis, pancreatitis, retinopathy, thrombocytopenic purpura, thyroid disease, urticarial, axonal and neuronal neuropathies, Balo disease, Behcet's disease, bullous pemphigoid, cardiomyopathy, Castleman disease, celiac disease, Chagas disease, chronic fatigue syndrome, chronic inflammatory demyelinating polyneuropathy, chronic

recurrent multifocal osteomyelitis, Churg-Strauss syndrome, cicatricial pemphigoid/benign mucosal pemphigoid, Crohn's disease, Cogans syndrome, cold allutinin disease, congenital heart block, Coxsacke myocarditis, CREST disease, essential mixed cryoglobulinemia, demyelinating neuropathies, dermatitis herpetiformis, dermatomyositis, Devic's disease, discoid lupus, Dressler' syndrome, endometriosis, eosinophilic esophagitis, eosinophilic fasciitis, erythema nodosum, experimental allergic encephalomyelitis, Evans syndrome, fibromyalgia, fibrosing alveolitis, giant cell arteritis, giant cell myocarditis, glomerulonephritis, Goodpasture's syndrome, granulomatosis with polyangiitis, Graves' disease, Guillain-Barre syndrome, Hashimoto's encephalitis, Hashimoto's thyroiditis, hemolytic anemia, Henoch-Schonlein purpura, herpes gestationis, hypogammaglobulinemia, idiopathic thrombocytopenic purpura, IgA nephropathy, IgG4-related sclerosing disease, immunoregulatory lipoproteins, inclusion body myositis, interstitial cystitis, juvenial arthritis, juvenial diabetes (Type 1 diabetes), juvenile myositis, Kawasaki syndrome, Lamber-Eaton syndrome, leukocytoclastic vasculitis, lichen planus, lichen sclerosus, ligneous conjunctivitis, linear IgA disease, lupus, lyme disease, Meniere's disease, microscopic polyangiitis, mixed connective tissue disease, Mooren's ulcer, Mucha-Habermann disease, multiple sclerosis, myasthenia gravis, myostitis, narcolepsy, neuromyelitis optica, neutropenia, ocular cicatricial pemphigoid, optic neuritis, palindromic rheumatism, PANDAS, paraneoplastic cerebellar degeneration, paroxysmal nocturnal hemoglobinuria, Parry Romber syndrome, Parsonnage-Turner syndrome, pars planitis, pemphigus, peripheral neuropathy, perivenous encephalomyelitis, pernicious anemia, POEMS syndrome, polyarteritis nodosa, Type I, II and III autoimmune polyglandular syndromes, polymyalgia rheumatic, polymyositis, postmyocardial infarction syndrome, postpericardiotomy syndrome, progesterone dermatitis, primary biliary cirrhosis, primary sclerosing cholangitis, psoriasis, psoriatic arthritis, idiopathic pulmonary fibrosis, pyoderma gengrenosum, pure red cell aplasia, Raynauds phenomenon, reactive arthritis, reflex sympathetic dystrophy, Reiter's syndrome, relapsing polychondritis, restless legs syndrome, retroperitoneal fibrosis, rheumatic fever, rheumatoid arthritis, sarcoidosis, Schmidt syndrome, scleritis, scleroderma, Sjogren's syndrome, sperm and testicular autoimmunity, stiff person syndrome, subacute bacterial endocarditis, Susac's syndrome, sympathetic ophthalmia, Takayasu's arteritis, temporal arteritis/giant cell arteritis, thrombocytopenic purpura, Tolosa-Hunt syndrome, transverse myelitis, Type 1 diabetes, ulcerative colitis,

undifferentiated connective tissue disease, uveitis, vasculitis, vesiculobullous dermatosis, vitiligo, and Wegener's granulomatosis.

EXAMPLES

[00354] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (e.g. amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Celsius, and pressure is at or near atmospheric. Standard abbreviations may be used, e.g., bp, base pair(s); kb, kilobase(s); pl, picoliter(s); s or sec, second(s); min, minute(s); h or hr, hour(s); aa, amino acid(s); kb, kilobase(s); bp, base pair(s); nt, nucleotide(s); i.m., intramuscular(ly); i.p., intraperitoneal(ly); i.n., intranasal(ly); i.v., intravenous(ly); s.c., subcutaneous(ly); M/ml, million units or 10^6 CFU/ml; M, million units/mouse or 10^6 CFU/mouse; and the like.

MATERIALS AND METHODS

[00355] The following materials and methods were used in the Examples described below.

Materials

[00356] RPMI serum-free media was obtained from the Life Technologies (Burlington, Ontario, Canada). RPMI was supplemented with 5-10% fetal bovine serum, sodium pyruvate, Penicillin-streptomycin and 2-mercapto-ethanol to make complete medium, which was used in various cell cultures. ConA, PWM and LPS were obtained from Sigma Chemical Company. Cytokine kits and fluorescent-labeled anti-mouse antibodies were purchased from eBioscience (San Diego, CA). Anti mouse FOXP3 was purchased from biolegend (San Diego, CA). Aldra cream (5% imiquimod) was obtained University of Alberta Hospital pharmacy. Wild-type and lipopolysaccharide (LPS)-negative *Caulobacter crescentus* (LPS^{-ve} CC) were grown at room temperature (22-27°C) in the incubator, and stored in saline at 4°C or room temperature for various time periods.

Wild-type *Caulobacter vibroides* (CV) was grown at room temperature (22-27°C) in the incubator, and stored in saline at 4°C or room temperature for various time periods.

Methods

Mice

[00357] 6-8 Weeks old C57BL/6 or 9-11 week BALB/c, male or female mice were purchased from Charles River Breeding Laboratories. All animal experimental protocols used in this study were approved by the University of Alberta Animal Care and Use Committee for Health Sciences, and conducted in accordance with the guidelines of the University of Alberta, Edmonton, Canada

Treatments of mice and sample collections

[00358] The mice were administered single or multiple times with Caulobacter crescentus (CC) in PBS using doses, schedule and routes as described in different examples and figure legends. CC used was prepared in two formats: CC-1 (CC grown in liquid PYE medium and stored at room temperature in saline), and CC-2 (CC grown in liquid PYE medium and stored at 4°C in refrigerator). CC-2 has also been referred to as CC in figures and description.

[00359] After euthanization of mice at specific times, blood, spleen, lungs, liver, lymph nodes, etc. were collected. Serum samples were used to determine biochemical markers using commercial Vet test kits (Idexx Laboratories).

Isolation of lymphocytes from spleen

[00360] At specific times after immunization, the mice were euthanized to obtain splenocytes. The spleens were pooled from 3-5 mice and ground to a single cell suspension and filtered through a Falcon 100 µm nylon cell strainer. After centrifugation, the cell pellet was resuspended in 2 ml of sterile distilled water and briefly vortexed. Immediately, 2× PBS were added and after a brief vortex the volume was made to 25 ml with 1× PBS. The tube was centrifuged and the cell pellet was resuspended in 10 ml of complete RPMI. It was again filtered through a Falcon 100 µm nylon cell strainer and centrifuged. The cell pellet was resuspended in 2 ml of RPMI media. These lymphocytes were used for the experiment.

Mouse cytokine ELISA

[00361] Cytokines and chemokines secreted in the supernatant of proliferating co-cultures, or mouse serum samples were measured using sandwich enzyme-linked immunosorbent assay (ELISA) kits following the manufacturer's protocol (eBioscience, CA, USA) for the presence of IL-10, GM-CSF, IL-17A, IFN-γ, TNF-α, IL-2, IL-6, IL-

1βIL-22, MIP-1α, IL-8/KC. A dilution of 1:2 to 1:50 was used for the samples with the standards ranging from 5 to 2,000 pg/ml. Finally the ELISA plates were read and the concentrations were calculated with an automated ELISA plate reader (Fluostar Optima, BMG Labtech).

Evaluation of antibody responses

[00362] The levels of antibodies (IgG, IgG2a, IgE) in serum and lung washes were determined using enzyme-linked immunosorbent assays (ELISAs). Briefly, 96-well nitrocellulose (Nunc) plates were coated with relevant antigen (such as OVA, MOG peptide) and incubated overnight at 4 °C. The plates were blocked with PBS containing normal mouse serum, followed by incubating with the experimental samples at different dilutions for 2 hrs at room temperature. After washing the plates for 4 times, Anti mouse Ig isotype antibodies conjugated with Alkaline phosphatase (AP) were added, followed by incubation for 2 hrs. After washing the plates, PNPP substrate was added and color development was read on Fluostar ELISA reader at 405 nm wavelength. All reagents for antibody detection were obtained from Southern Biotech (Birmingham, AL).

T cell proliferation assay

[00363] Proliferative responses of splenic T cells were measured in triplicate cultures in 96-well flat-bottomed microtiter plates. A total of 4×10^5 spleen T cells from immunized mice and 4×10^5 antigen-presenting cells (APCs) (spleen cells from control syngeneic mice irradiated with 18 Gy) were mixed with different concentrations (0.1, 1 and 10 μg/mL) of MOG peptide were cultured in RPMI medium (with 10% fetal bovine serum (FBS)) at 37°C (5% CO_2) for 4 days.

[00364] The cells were pulsed with 0.5 μCi/well [^{3}H]-thymidine (Amersham) for 12-18h and harvested on filter papers (Perkin Elmer). The levels of [^{3}H]-thymidine incorporated into the DNA of proliferating cells were counted in a Microbeta Trilux liquid scintillation counter (Perkin Elmer). Proliferation is represented as the mean cpm ± SE (standard error) of triplicate cultures.

Flow cytometry analysis of surface markers, intracellular IL-10 and Foxp3

[00365] A total of 5 ×105 cells from immunized mice were taken for intracellular and extracellular staining with multicolor fluorescently labeled mAbs (concentrations according to manufacturer's instructions). The cells were incubated with Fc mouse-serum (Sigma) to prevent non-specific binding and washed with fluorescence-activated cell sorter (FACS)-buffer (2 % fetal bovine serum in 1× phosphate-buffered saline (PBS). After incubation for 30 minutes with anti-mouse CD3e-FITC, CD4-PECy-5, CD25-PE-

Cy7, CD8a-APC-Cy7, anti-PD-1-PerCP eFluore 710, anti-CD49b-Alexafluor-700 (for BALB/c and C57bl/6 mice) etc. (eBioscience) for extracellular markers at 4°C, the cells were washed twice and fixed in fixative solution (1 % paraformaldehyde in FACS-buffer) for 5 minutes. After washing twice, the cells were incubated with cold permeabilization buffer (FACS-buffer + 0.3% Saponin (Sigma) + 5 % normal human serum in PBS) for 5 minutes followed by addition of anti-mouse IL-10 (eBioscience) and anti-Foxp3-PE (biolegend) and further incubated for 30 minutes at 4°C. The cells were washed once with FACS-buffer containing 1 % Saponin and fixed. They were read in Fortessa and analyzed using FACS-DIVA software (Becton Dickinson, Mountain View, CA). Each marker was gated based on its respective isotype-matched control monoclonal antibodies.

Human PBMCs and DCs

[00366] Peripheral blood mononuclear cells (PBMCs) were obtained from normal human donors using Ficoll-Paque. To obtain dendritic cells (DCs), adherent PBMCs were cultured with recombinant GM-CSF and IL-4 for 5-6 days in RPMI media, using procedures well established in the literature. Human PBMCs cultured with test materials for specified times as described in individual examples were stained with antibodies against CD34, CD45, CD11c and CD11b, labeled with various fluorophores obtained commercially (eBiosciences), using standard procedures.

RESULTS

[00367] The following examples are intended to illustrate rather than limit the scope of the invention.

[00368] The immunomodulatory effects of CC were tested alone and with different antigens in different models and indications via systemic and mucosal routes as follows.

Example 1: Effect of *Caulobacter crescentus* (CC) on modulation of inflammatory cytokines in concanavalin A (ConA) stimulated splenocytes upon oral and intranasal administration of CC in healthy mice

[00369] C57/bl6 male mice were treated twice weekly orally or intranasally for five times with CC at 500x106 CFU/mouse or PBS control. Mice were euthanized 8 days after the last treatment. The spleens isolated and ex-vivo stimulated with T cell mitogen ConA at 1ug/ml concentration for 24 hrs. Supernatant were collected and cytokines (IFN-γ, TNF-α, IL-6, and IL-17A) were measured using ELISA (FIG. 1). These results demonstrate that treatment with CC down-regulates production of inflammatory cytokines in splenocytes upon ex-vivo stimulation with Con A and suggest the role of CC in suppressing inflammation mediated by T cells from a variety of infections including

viral, bacterial, fungal as well as from environmental toxins, drug reactions and autoimmune disorders.

Example 2: Effect of Caulobacter crescentus (CC) on modulation of inflammatory cytokines from pokeweed (PWM) stimulated splenocytes upon oral and intranasal administration of CC in healthy mice

[00370] C57/bl6 male mice were treated twice weekly orally or intranasally for five times with CC at 500x106 CFU/mouse or PBS control. Mice were euthanized 8 days after the last treatment. The spleens of treated mice were isolated and ex-vivo stimulated with a B cell mitogen PWM at 0.1ug/ml concentration for 24 hrs. Supernatant were collected for cytokines (IFN-γ, TNF-α, IL-6 and IL-17A) measurements using ELISA (FIG. 2). These results demonstrate that treatment with CC down-regulates production of inflammatory cytokines in splenocytes upon ex-vivo stimulation with PWM and suggest the role of CC in reducing excessive production of proinflammatory cytokines in infection and non-infection related systemic inflammatory disorders.

Example 3: Effect of *Caulobacter crescentus* (CC) on induction of anti-inflammatory cytokine IL-10 in vivo upon oral and intranasal administration:

[00371] Groups of five C57/bl6 male mice were treated twice weekly orally or intranasally for five times with CC at $500x10^6$ CFU/mouse or PBS control. Mice were euthanized 8 days after the last treatment and spleens were isolated. Splenocytes were cultured with media, ConA and PWM for 24 hr. Supernatant were collected for IL-10 measurement using ELISA (FIG. 3A- FIG. 3C). The results obtained demonstrate that CC up-regulates IL-10 production ex-vivo in splenocytes upon 24 hr culture with or without stimulants and suggest that CC can induce IL-10 production in vivo. These results also indicate systemic immunomodulatory and anti-inflammatory role of CC in reestablishing homeostatic balance in inflammatory conditions.

[00372] Overall, results described in FIG. 1, FIG. 2, and FIG. 3 suggest that CC has capacity to induce higher levels of the anti-inflammatory cytokine IL-10 and down-regulate levels of inflammatory cytokines IFN-γ, TNF-α, IL-6 and IL-17A. Pro-inflammatory cytokines play a major role in the pathogenesis of many diseases and hence there is an interest in developing therapeutics to modulate their excessive production in a range of afflicted diseases.

Example 4: Effect of *Caulobacter crescentus* (CC) on IL-10 production from ex vivo LPS-stimulated splenocytes isolated from CC treated mice:

[00373] Female C57/bl6 mice were treated twice weekly orally via gavage for four times with CC at $500x10^6$ CFU/mouse or PBS control. Mice were euthanized 4 days after the last treatment and spleens were collected. Splenocytes were stimulated with LPS at 1ug/ml concentration for 24 and 72 hrs. Supernatants were collected and IL-10 was measured using ELISA (FIG. 4). The results obtained demonstrate that CC upregulates IL-10 production ex-vivo in splenocytes upon LPS stimulation compared to placebo group (PBS). These studies suggest the anti-inflammatory activity of CC in normalizing the dysregulated release of pro-inflammatory cytokines and protection against inflammatory responses and/or autoimmune disorders.

Example 5: Effect of *Caulobacter crescentus* (CC) on pro-inflammatory cytokines in gut-associated mesenteric lymph nodes upon oral treatment:

[00374] In order to determine the effect of CC on inflammatory cytokines levels in intestinal lymphoid tissue, female C57/bl6 mice were treated twice weekly orally for four times with CC at $500x10^6$ CFU/mouse or PBS control. Three days after the last treatment, mice were euthanized and local mesenteric lymph nodes were collected. Cytokines levels were determined in supernatant collected after 24 hr LPS stimulation. Oral administration of CC led to decrease in the levels of IFN-γ, IL-6 and IL-17A compared to PBS group (FIG. 5). These results demonstrated that CC can down-regulates production of Th1 and Th17 cytokines in local mesenteric lymph nodes. Thus, CC has ability to reduce TH1 and/or TH17 mediated pro-inflammatory cytokine levels in a variety of inflammatory disorders where immune dysregulation and inflammation is triggered by external or internal stimuli or microorgamisms such as Gram+ and Gram- bacteria, viruses, fungi, parasites, LPS, toxins, autoantigens, glycosylphosphatidyl-inositol, tissue injury (trauma, burns) etc.

Example 6: Effect of *Caulobacter crescentus* (CC) in systemic immune modulation in mice after oral treatment:

[00375] Female C57/bl6 mice were treated orally twice weekly for four times with CC at $500x10^6$ CFU/mouse or PBS control. Mice were euthanized 4 days after the last treatment and spleens were collected. The percentage of CD3+CD4+ and CD3+CD8+ cells expressing IL-10^+ were analyzed by flow cytometry. Treatment with CC led to increased expression of intracellular IL-10 on both $CD4^+$ and $CD8^+$ T cells in splenocytes (FIG. 6). Taken together, the results shown in FIG.4-FIG. 6 demonstrate that CC has strong ability

to normalize immune dysregulation both locally and systemically in inflammatory and autoimmune disorders.

Example 7: Effect of *Caulobacter crescentus* (CC) on modulation of pro-inflammatory cytokine production in spleen after subcutaneous treatment:

[00376] Groups of three C57/bl6 male mice were administered with CC ($500x10^6$ CFU/mouse) or PBS once weekly for four weeks by subcutaneous route. Mice were euthanized 28 days after the last treatment. Spleens were harvested and splenocytes were cultured with ConA. Cytokines levels were determined in supernatant collected after 24 hr ConA stimulation. The results presented in FIG. 7 show that CC led to persistent modulation in the production of IFN-γ, TNF-α andIL-6 cytokines (FIG. 7). Thus, CC can provide long-lasting immunomodulatory effect even after cessation of therapy.

Example 8: Modulation of innate and adaptive immune cells after oral treatment with *Caulobacter crescentus* (CC):

[00377] Groups of three C57/bl6 male mice were treated orally with CC ($500x10^6$ CFU/mouse) or PBS once weekly for four weeks. Mice were euthanized 28 days after the last treatment and splenocytes were harvested and analyzed by flow cytometry. Oral treatment with CC led to increased FOXP3 expression on $CD8^+$, $CD8^+CD25^+$ and NKT ($CD3^+CD49b^+$) cells and increased PD-1 expression on NK cells (FIG. 8). Thus CC induces various regulatory lymphocytes to control inflammation. This data suggest that CC can induce homeostasis by regulating the expression of different regulatory molecules on innate and adaptive immune cells and therefore, CC can be used to control excessive inflammation in various diseases. PD-1 expression on NK cells has been shown to control inflammatory responses in mycobacterial infection. In addition, PD-1 on NK has also shown to protect from inflammation including viral, bacterial and autoimmune disorders.

[00378] NK and/or NKT cells have been shown in down regulating autoimmune responses in several diseases including multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, autoimmune thyroid disease, psoriasis, Behcet's disease, type I diabetes, neurodegenerative disease etc. Therefore, the present disclosure represents attractive biotherapeutic for the prevention and/or treatment of a range of inflammatory, allergic and autoimmune disorders. Thus, overall the present disclosure represents a strategy to prevent and/or treat systemic and local inflammation in infectious and non-infectious settings through modulating the activity of adaptive and innate T and/or NK and/or NKT cells.

Example 9: Modulation of T cells in splenocytes after subcutaneous treatment with *Caulobacter crescentus* (CC):

[00379] Groups of three C57/bl6 male mice were treated subcutaneously with CC ($500x10^6$ CFU/mouse) or PBS once weekly for four weeks. Mice were euthanized 28 days after the last treatment and splenocytes were harvested and analyzed by flow cytometry. Subcutaneous treatment with CC led to increased FOXP3 expression on $CD4^+$, $CD4^+CD25^+$, $CD8^+$ and $CD8^+CD25^+$ T cells (FIG. 9). Thus parenteral administration of CC can also provide long-lasting immunomodulatory effects. These results demonstrate the effect of CC in inducing and expanding subsets of regulatory T cells. T regulatory cells have been shown to suppress inflammatory activity in a wide range of diseases including autoimmune encephalomyelitis, IBD, bacterial-induced colitis, type 1 diabetes, airway eosinophilic inflammation, graft vs. host disease, organ transplantation etc.

Example 10: *Caulobacter crescentus* (CC) exhibits positive benefits in controlling systemic inflammation in LPS challenged model of sepsis/inflammation: Modulation of cytokine levels in serum.

[00380] Groups of 3 C57/bl6 male mice were challenged with LPS at 7 mg/Kg in 100 µl PBS intraperitonially and treated orally with CC ($500x10^6$ CFU/mouse) post 2 and 24 hr in vivo challenge with LPS. Healthy unchallenged and PBS fed mice were also included as controls. Mice were euthanized after the second treatment and blood samples were collected and analyzed for cytokines by ELISA. The LPS challenged mice had high levels of inflammatory cytokines in sera. In contrast, CC treatment down-regulated production of inflammatory cytokines IL-1β and IL-6 and up-regulated the production of anti-inflammatory cytokine IL-10 (FIG. 10). Thus, CC promotes non-damaging immune responses. Induction of IL-1β and IL-6 has been associated with a number of acute and chronic inflammatory and auto-immune diseases such as sepsis, MS, Alzheimers, Parkinsons, RA, gout, metabolic diseases (atherosclerosis, type II diabetes,), hypertension, chronic obstructive pulmonary disease (COPD), asthma, psoriasis and allergy. Therefore, CC could help in managing and ameliorating these inflammatory medical conditions.

Example 11: *Caulobacter crescentus* (CC) exhibits positive benefits in controlling local inflammation in a sepsis/inflammation model: Modulation of cytokine levels in lungs and liver.

[00381] Groups of 3 C57/bl6 male mice were challenged with LPS at 7mg/Kg in 100 µl PBS intraperitonially and treated orally with CC (500x106 CFU/mouse) post 2 and 24 hr in vivo challenge with LPS. Healthy unchallenged and PBS fed mice were also included as controls. In these studies, CC used was prepared in two formats: CC-1 (CC grown in liquid PYE medium and stored at room temperature in saline), and CC-2 (CC grown in liquid PYE medium and stored at 4°C in refrigerator). Mice were euthanized after 2nd treatment of CC-1 and CC-2, and lungs and liver were harvested followed by determining cytokines in their homogenates. Both CC-1 and CC-2 down-regulated production of inflammatory cytokines TNF-α, IL-6, IL-1β and IL-17A in lungs and liver, compared to LPS challenged group (FIG.11). These results demonstrate that CC can be utilized in controlling inflammatory processes and normalizing tissue functions including post-inflammmatory medical conditions related to viral and bacterial pathogens, tissue damage, cellular stress, metabolic perturbations etc. in various (intestine, lung, liver, brain, skin, heart etc.) organs. LPS mediated sepsis is a common cause of fatality in critical care, surgical and burn units. Therapeutic approaches directed towards ameliorating LPS mediated fatal inflammatory cascade through targeting host immune components could have clinical and therapeutic advantages.

Example 12: *Caulobacter crescentus* (CC) exhibits positive effects on biochemical parameters of liver damage in LPS challenged mouse model of inflammation:

[00382] Groups of 3 C57/bl6 male mice were challenged with LPS at 7mg/Kg in 100 µl PBS intraperitonially and treated orally with CC ($500x10^6$ CFU/mouse) post 2 and 24 hr in vivo challenge with LPS. Healthy unchallenged and PBS fed mice were also included as controls. In these studies, CC used was prepared in two formats: CC-1 (CC grown in liquid PYE medium and stored at room temperature in saline), and CC-2 (CC grown in liquid PYE medium and stored at 4°C in refrigerator). Mice were euthanized after 2nd treatment of CC-1 and CC-2, and blood samples were collected to determine the effects on biochemical markers. Treatment with both CC-1 and CC-2 normalized the serum levels of glucose (GLU), globulin (GLOB), alanine aminotransferases (ALT), total phosphates (TP) and total bilirubin (TBIL) of LPS challenged mice to the levels of non-challenged and PBS fed mice (FIG. 12). These results demonstrate that CC could be

used effectively in treating various inflammation mediated disorders including liver associated diseases.

Example 13: *Caulobacter crescentus* (CC) prevents liver injury in LPS challenged mice model:

[00383] Groups of 3 C57/bl6 male mice were challenged with LPS at 7mg/Kg in 100 µl PBS intraperitonially and treated orally with CC ($500x10^6$ CFU/mouse) post 2 and 24 hr in vivo challenge with LPS. Healthy unchallenged and PBS fed mice were also included as controls. In these studies, CC used was prepared in two formats: CC-1 (CC grown in liquid PYE medium and stored at room temperature in saline), and CC-2 (CC grown in liquid PYE medium and stored at 4°C in refrigerator). Mice were euthanized after 2nd treatment of CC-1 and CC-2 and various organs were collected. No inflammation or damage to lung, liver and other organs was observed with both CC-1 and CC-2. H & E staining of liver sections were performed. The results shown in FIG. 13 demonstrate a protective effect of CC administered by oral route in the prevention of LPS induced inflammation and liver damage, compared to LPS challenged mice. Massive destruction of liver has been associated with a number of medical conditions due to undesirable inflammatory activities as a result of infectious and non-infectious pathogenesis. Therefore, CC has strong potential in preventing and ameliorating liver damage from autoimmune hepatitis, alcohol related hepatic disorders, viral mediated hepatitis etc.

Example 14: Modulation of cytokines in imiquimod (IMQ)-induced psoriasis-like dermatitis mouse model upon oral treatment with *Caulobacter crescentus* (CC):

[00384] 10-11 Weeks old Balb/c female mice were administered a topical dose of 6.25 mg of 5% IMQ cream (Aldra, Imiquimod) for 6 consecutive days on shaved back. Mice were treated orally with CC at $500x10^6$ CFU/mouse from day 3 (5 days a week for two weeks). Mice were euthanized 3 days after the last treatment and spleens were harvested. Splenocytes were cultured ex vivo with medium for 4 days and culture supernatants were examined for cytokines (FIG. 14). Treatment with CC led to a reduction in the production of IFN-γ, IL-6, IL-17A and IL-22 in Aldra induced psoriasis mice compared to PBS treated psoriatic mice (FIG. 14). These studies suggest that CC can correct cytokine dysregulation in inflammatory and autoimmune diseases and lead to beneficial therapeutic effects. Besides psoriasis, infiltration of immune cells in the dermis and epidermis also occur in other chronic skin diseases such as atopic dermatitis, acne inversa, rosacea etc. Therefore, CC can be used in treating various skin disorders with an inflammatory component. Taken together, the results presented in Figure 14 demonstrate

that CC has systemic immunomodulatory and anti-inflammatory activity to protect against pathogen or autoimmune associated inflammatory responses.

Example 15: Effect of *Caulobacter cescentus* (CC) in reducing pro-inflammatory cytokines and chemokines in colon tissues of DSS-induced inflammatory bowel disease (IBD) afflicted mice.

[00385] Groups of 5 male C57bl/6 were given 3% dextran sulfate sodium (DSS) in drinking water for 7 consecutive days. Mice were treated with CC ($500x10^6$ CFU/mouse) on the same day DSS was started. Water treated mice were used as controls. On day 10, mice were euthanized and colon tissues were harvested and cultured for 24 h. Cytokines were determined in culture supernatants using ELISA. The results obtained indicate that CC reduced pro-inflammatory cytokines IFN-γ, TNF-α, IL-1β, and chemokines IL-8/KC and MIP-1α (FIG 15). Thus, oral treatment of CC attenuated aberrant levels of inflammatory cytokines and chemokines locally in colon in the murine DSS-induced colitis model for IBD, which account for activation of cascades leading to epithelial permeability, apoptosis, ulceration, diarrhea etc. in IBD.

Example 16: Effect of *Caulobacter crescentus* (CC) in suppressing auto-antigen specific T cell and antibody responses in experimental autoimmune encephalomyelitis (EAE) model.

[00386] To determine the effect of CC in reducing auto-antigen specific immune responses, groups of five C57Bl6 female mice were immunized with 200μg MOG_{35-55} peptide emulsified in CFA in 100 μl saline subcutaneously. Additionally, mice received 400 ng of pertussis toxin in 200 μl saline intraperitoneally at day 0 and 3. Starting from day 3 of immunization, mice were treated orally with CC ($500x10^6$ cfu/mouse) continuously every 3rd day till the end of the experiment. PBS treated challenged mice were used as controls. Mice were euthanized 30 days after immunization and spleen and blood samples were collected. T cell responses were examined in splenocytes against MOG peptide (10, 1 and 0.1 μg/ml). Anti-MOG antibody (IgG and IgG2a) titers were analyzed by ELISA in serum samples. Interestingly, CC reduced autoantigen-MOG-specific T cell responses compared to PBS control group (FIG. 16). CC also reduced the autoantigen-MOG-specific IgG and IgG2a antibody titers compared to PBS control group (FIG. 16). These results suggest that CC can reduce autoantigen specific T and B cell responses. EAE model is a commonly used model for the human inflammatory demyelinating disease, multiple sclerosis (MS). MS is an inflammatory disease of the central nervous system (CNS). EAE is a complex condition where interaction between

immunopathological and neuropathological mechanisms leads to pathological features of MS, viz., inflammation, demyelination, axonal loss and gliosis. Therefore, CC can be effective in treating autoimmune and neurological disorders, autoimmune blood diseases, autoimmune hemolytic anemia etc..

Example 17: Effect of *Caulobacter crescentus* (CC) in reducing allergen (OVA)-specific antibody and cytokine responses in a mouse model of Ovalbumin-induced airway inflammation model.

[00387] To determine the effect of CC in airway/lung inflammatory diseases, groups of 5 Balb/c male mice were sensitized on day 1 and day 6 with 10 µg ovalbumin and 2 mg $Al(OH)_3$ in 400 µl saline intraperitoneally. Mice were challenged intranasally (15 µl/nostril) with 50 µg ovalbumin on days 12 and 14. From day 7 onwards of sensitization, mice were treated orally with CC ($500x10^6$ CFU/mouse) every third day up to day 17. In separate groups, mice were treated with dexamethasone (DEX, 2 mg/Kg, i.p.) alone once on day 13 or dexamethasone and CC. Control mice received saline at the same schedule as CC. Mice were euthanized next day of the last treatment, blood samples, lung washes and spleen were collected. A single cell-suspension ($2x10^6$ cells/ml) of splenocytes was cultured with 50 µg OVA for 96 h and cytokines (IL-4 and IL-6) levels were analyzed in culture supernatants by ELISA. Oral treatment with CC reduced the production of OVA specific IgEs in serum and lung washes in mice sensitized with OVA (Fig. 17). It was found that levels of IL-4 and IL-6 were also reduced in spleen by CC treatment (Fig. 18). Combining CC treatment with dexamethasone led to further reduction in IL-4 and IL-6 levels in spleen compared to dexamethasone alone treatment (Fig. 19). These data suggest that treatment with CC prevents OVA-induced allergic airway inflammation in mice. Allergy is a complex disease where multiple immune cells and inflammatory mediators contribute to the initiation and manifestation of allergic diseases. Allergies are most frequently the results of IgE-mediated hypersensitivity reactions. Increased production of IL-4 and IL-6 has been correlated with the allergic diseases. The presence of IgE in serum is a hallmark of allergic diseases driven by IL-4 mediated Ig class switching in B cells. IgE dependent allergic reactions may affect one or more target organs and allergic diseases such as rhinitis, sinusitis, conjunctivitis, asthma, dermatitis, and food allergies etc.

Example 18: Effect of *Caulobacter crescentus* (CC) in treating metabolic disorders and reducing systemic inflammation in high-fat diet induced obesity model.

[00388] Groups of five C57bl/6 mice were fed high-fat diet for 4-6 months and treated with CC ($500x10^6$cfu/mouse) thrice weekly for 4-6 months. PBS treated high-fat diet fed mice were used as controls. Glucose tolerance test was performed prior to terminating the experiment at ~180 days. Blood glucose was measured using OneTouch monitoring system. Mice were euthanized and blood, liver and spleen were collected. Serum samples were used to determine biochemical parameters by Vet test. Liver homogenates were prepared and pro-inflammatory cytokines (IFN-γ, TNF-α, IL-6, IL-1β) were determined by ELISA. Splenocytes ($2x10^6$ cells/ml) were cultured with LPS (1mg/ml) for 24 h and cytokines (IFN-γ, TNF-α, IL-6) were analyzed in culture supernatants by ELISA. Oral treatment with CC significantly reduced pro-inflammatory cytokines in liver (FIG. 20) and spleen (FIG. 21) compared to high-fat diet control mice, suggesting that CC can effectively reduce chronic and systemic inflammation. Oral treatment with CC also provided positive benefits in biochemical parameters associated with metabolic diseases in high-fat diet induced obesity model (FIG. 22). Further mice on CC treatment demonstrated improved glucose tolerance compared to control group (FIG. 23). It has been well established that obesity is associated with low-grade inflammation contributing to a number of metabolic disorders including type 2 diabetes mellitus, cardiovascular diseases, hypertension, hypercholesterolemia, hypertriglyceridemia, non-alcoholic fatty liver disease, hair loss etc. In obese state, production of a number of inflammatory cytokines and chemokines (e.g., IFN-γ, TNF-α, IL-6, IL-1β etc.) is dysregulated. Obesity is also associated with insulin resistance leading to glucose intolerance, and non-alcoholic fatty liver disease. It has been shown that inhibition of the activity of TNF-α also significantly inhibits the development of steatohepatitis in alcohol-fed animals. High cholesterol is associated with elevated risks of coronary heart disease (atherosclerosis), stroke, peripheral vascular diseases, diabetes, and high blood pressure. Elevated levels of triglycerides are associated with atherosclerosis and also increase the risk of acute pancreatitis. A high uric acid level occurs when kidneys do not eliminate uric acid efficiently. Other factors that may cause high uric acid include obesity, hypothyroidism etc. Build up of uric acid can lead to inflammation and intense pain of a gout attack. An elevated level of creatine kinase is seen in heart attacks, all types of muscular dystrophy, endocrine disorders, neuromuscular diseases etc. Pro-inflammatory cytokines such as TNF-α, IL-6, IFN-γ, IL-1β are known to be involved in obesity, obesity-related

pathologies such as type 2 diabetes, insulin-resistance, non-alcoholic fatty liver disease, alcohol-induced liver disease, vascular dysfunction related neurodegenerative processes such as Alzheimer disease, neuropsychiatric disorders such as depression, schizophrenia etc. Mitochondrial reactive oxygen species (ROS) drive pro-inflammatory cytokine (TNF-α, IL-6, IFN-γ, IL-1β) production in chronic human diseases. These studies show that treatment with CC reduces serum biochemical markers associated with metabolic disorders, improves glucose tolerance and reduces pro-inflammatory cytokines in liver in obese mice on high-fat diet.

Example 19: Effect of *Caulobacter crescentus* (CC) in reducing hepato- and nephro-toxicities associated with anticancer drug cyclophosphamide in EL-4 lymphoma-bearing mice.

[00389] To determine the effect of CC in reducing toxicities associated with a therapeutic treatment, groups of five C57Bl6 mice were challenged with $0.25x10^6$ EL-4 cells/mouse in 100 µl saline subcutaneously in the lower left flank. Starting from day 5 post challenge with EL-4 cells, CC ($50x10^6$cfu/mouse) was administered once weekly orally. On days seventeen and twenty-one, mice were treated with cyclophosphamide at 150 mg/Kg intraperitoneally. Healthy unchallenged and cyclophosphamide alone treated challenged mice were used as controls. Mice were humanely euthanized 30 days after EL-4 challenge and blood samples were collected. Treatment with CC along with cyclophosphamide normalized the serum levels of phosphate (PHOS) and total bilirubin (TBIL) in EL-4 tumor bearing mice to the levels of non-challenged normal mice (FIG. 24). These results demonstrate that CC could be used effectively in reducing toxicities of anticancer agents or a therapeutic treatment.

Example 20: Effect of *Caulobacter crescentus* (CC) in reducing organ toxicities associated with anticancer drug cisplatin in B16 metastatic cancer model.

[00390] To determine the effect of CC in reducing toxicity associated with cancer chemotherapy, groups of five C57Bl6 mice were challenged with $0.4x10^6$ B16 cells/mouse in 100 µl saline intraperitoneally. Mice were treated with cisplatin (4 mg/kg) intraperitoneally at days 7 and 10 post B16 challenge and CC ($50x10^6$cfu/mouse) was administered orally once weekly. Healthy unchallenged and cisplatin alone treated challenged mice were used as controls. Mice were euthanized 30 days after B16 challenge and blood samples were collected to determine the effects on serum biochemical markers. Treatment with CC along with cisplatin normalized the serum levels of phosphate (PHOS), urea, total bilirubin (TBIL) and aspartate aminotransferase

(AST) in B16 metastatic cancer bearing mice to the levels of non-challenged normal mice (FIG. 25). These results demonstrate that CC could be used effectively in reducing toxicities of anticancer agents or a therapeutic treatment.

Example 21: Effect of *Caulobacter crescentus* (CC) in reducing elevated levels of biochemical parameters of hepatotoxicity associated with checkpoint inhibitor antibody (anti-PD-1) in mouse model of B16 melanoma.

[00391] To determine the effect of CC in reducing toxicities associated with therapeutic antibodies, groups of five C57Bl6 mice were challenged with $0.4x10^6$ B16 cells/mouse in 100µl saline subcutaneously in the lower left flank. Starting from day 3 post challenge with B16 melanoma cancer cells, CC ($50x10^6$cfu/mouse) was administered orally once weekly. Two days after first treatment with CC, anti-PD-1 antibody (200ug/mouse) was administered intraperitoneally and continued every 3-4 days. Healthy unchallenged and anti-PD-1 antibody alone treated challenged mice were used as controls. Mice were euthanized 25 days after tumor challenge and blood samples were collected to determine the effects on biochemical markers. Treatment with CC along with anti-PD-1 monoclonal antibody normalized the serum levels of phosphate alanine aminotransferases (ALT) and aspartate aminotransferase (AST) in B16 tumor bearing mice to the levels of non-challenged normal mice (FIG. 26). These results demonstrate that CC could be used effectively in reducing toxicities of therapeutic and checkpoint inhibitor antibodies or a therapeutic treatment.

Example 22: LPS negative *Caulobacter crescentus* (LPS^{-ve} CC) protects mice from liver damage in LPS challenged model of sepsis/inflammation: modulation of cytokine levels in liver.

[00392] To determine the role of lipopolysaccharide negative (LPS^{-ve}) CC in immune modulation, C57/bl6 female mice were challenged with LPS at 25 mg/Kg in 200 µl saline intraperitonially and treated orally with LPS^{-ve} CC ($500x10^6$ CFU/mouse) post 2 and 20h in vivo challenge with LPS. Healthy unchallenged and PBS fed mice were also included as controls. Mice were euthanized after 24h of the second treatment, and liver was harvested followed by determining cytokines in their homogenates. LPS challenged mice had high levels of inflammatory cytokines and chemokines in liver homogenate. In contrast, LPS^{-ve} CC treatment down-regulated production of inflammatory cytokines IFN-γ, TNF-α, IL-1β, IL-6, IL-8/KC, and chemokine MIP-1α and up-regulated the production of anti-inflammatory cytokine IL-10 (FIG. 27). These results demonstrate that LPS^{-ve} CC also exhibits positive effect in controlling inflammatory processes, similar to those

obtained using wild-type CC. Therefore, LPS negative CC can be utilized in controlling inflammatory processes and normalizing tissue functions including post-inflammatory medical conditions.

Example 23: Effect of *Caulobacter vibroides* (CV) in reducing pro-inflammatory cytokines induced by a probiotic or pathogenic bacteria in human PBMCs.

[00393] Human PBMCs ($4x10^6$/well) were stimulated with inactivated *Lactobacillus rhamnosus* (LB) or *Lysteria monocytogenes* (LM) ($50x10^6$ CFU/ml) for 6 h. After that CV ($250x10^6$ CFU/ml) was added and plates were incubated for additional 24 or 96 h. Culture supernatants were collected and assayed for IFN-γ and TNF-α by ELISA. Treatment with CV reduced the levels of IFN-γ and TNF-α induced by LB and LM (FIG. 28). These results suggest that other species of Caulobacter can reduce the inflammation related to bacterial or viral pathogens. These results also suggest that Caulobacter species can be used to treat undesirable inflammatory responses induced by microbiome related and unrelated microbes. Further, they can be used to modulate immunomodulatory activity of a microbiome therapeutic.

Example 24: Effect of *Caulobacter cescentus* (CC) in *ex vivo* manipulation of human myeloid dendritic cells.

[00394] Human myeloid dendritic cells differentiated from peripheral blood monocytes ($2x10^6$/ml) were cultured for 24 h in the absence and presence of CC (50 or 10 CFU/ml). Culture supernatants were collected and examined for IL-10 levels by ELISA. The results obtained suggest that CC can generate a population of modulated DCs producing IL-10 (FIG. 29). Dendritic cells (DCs) are key regulators of adaptive immunity with the potential to induce T cell suppression and tolerance. IL-10 produced by DCs plays a role in generation, expansion and maintenance of regulatory T cells. These results suggest that CC can be used for *ex vivo* manipulation of DCs for DC-based immunotherapeutic strategies.

Example 25: Effect of *Caulobacter cescentus* (CC) on differentiation/expansion of pluripotent stem cells from human PBMCs into myeloid cells.

[00395] Human PBMCs ($4x10^6$/well) were cultured with CC ($500x10^6$, $50x10^6$, $10x10^6$ and $1x10^6$ CFU/ml) and saline for 10 days. PBMCs were stained for surface markers CD34, CD45, CD11c and CD11b. Cells were gated for CD34+CD45- pluripotent stem cells, which were further gated for CD11c+ and CD11b+ DCs and macrophages, and data were analyzed by flow cytometry. The results obtained suggest that CC can differentiate stem cells into myeloid cells (FIG. 30). Myeloid cells originate from multipotent

hematopoietic stem cells. These cells play a critical role in innate and adaptive immunity, inflammatory reaction, restoration of immune homeostasis, bone remodelling etc. Thus, CC can lead to differentiation and/or expansion of myeloid cells from stem cells for use in patient specific immunotherapy.

CLAIMS

What is claimed is:

1. An immunomodulatory composition comprising:

a) live *Caulobacter crescentus*; and

b) a pharmaceutically acceptable excipient.

2. The composition of claim 1, further comprising an antigen, an autoantigen, or an allergen.

3. The composition of claim 1 or claim 2, wherein the *Caulobacter crescentus* is wild-type, a lipopolysaccharide-negative strain or an S-layer-negative strain.

4. The composition of any one of claims 1-3, wherein the *Caulobacter crescentus* is viable, non-denatured, mutated, attenuated, or genetically modified.

5. The composition of any one of claims 1-3, wherein the *Caulobacter crescentus* is genetically modified to produce one or more heterologous polypeptides, wherein heterologous polypeptide is selected from an autoantigen, an allergen, a cytokine, a costimulatory or coinhibitory molecule, a chemokine, an immunoglobulin or an antigen-binding fragment thereof, an anti microbial agent.

6. The composition of any one of claims 1-5, further comprising a therapeutic antibody.

7. The composition of any one of claims 1-6, further comprising a probiotic, symbiotic, a therapeutic pathogen, or a therapeutic bacterium from microbiome of a patient.

8. The composition of any one of claims 1-6, further comprising at least one adjuvant, a cytokine, or a therapeutic agent selected from an anti-inflammatory agent, an anti-proliferative agent, a cytotoxic agent, an immunosuppressive agent, an immunoregulatory agent, immunomodulatory agent, an anti-histaminic agent, or an anti-microbial agent.

9. A method of modulating an immune response in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of any one of claims 1-8.

10. The method of claim 9, wherein the immune response comprises modulation of one or more cytokines.

11. The method of claim 9, wherein the immune response is a humoral immune response, a cellular immune response, or an innate immune response.

12. The method of claim 9, further comprising administering to the individual an autoantigen or an allergen.

13. The method of claim 9, further comprising administering to the individual a therapeutic treatment such as radiation therapy, laser therapy, photodynamic therapy and/or surgery.

14. The method of claim 9, further comprising administering to the individual an anti-bacterial agent, an anti-mycobacterial agent, an anti-protozoan agent, an anti-malarial agent, an anti-helminth agent, antiviral agent, anti-histaminic agent, anti-diabetes agent, anti-inflammatory agent, anti-proliferative agent, cytotoxic agent, immunosuppressive agent or an immunomodulatory agent.

15. The method of claim 9, further comprising administering to the individual an antibody.

16. The method of claim 9, further comprising administering to the individual a cytokine, an adjuvant, or an immunoregulatory agent.

17. The method of claim 9, further comprising administering to the individual a probiotic, a symbiotic, a therapeutic member from microbiome or a therapeutic pathogen.

18. The method of any one of claims 9-17, wherein the individual is a human, a non-human mammal, or a non-mammalian animal.

19. The method of any one of claims 9-18, wherein the composition is administered via an oral, nasal, subcutaneous, intramuscular, intravenous, vaginal, transdermal, topical, rectal, ocular, or mucosal route of administration.

20. A method of modulating dendritic cells, the method comprising:

a) contacting dendritic cells (DCs) obtained from an individual with a composition comprising: i) *Caulobacter crescentus*; and/or ii) an antigen, wherein said contacting is *in vitro* and wherein said contacting modulates antigen presentation of the antigen on the DCs, thereby generating a population of modulated DCs.

21. The method of claim 20, further comprising administering the modulated DCs to the individual.

22. A method of generating regulatory lymphocytes, wherein the regulatory lymphocytes are natural killer (NK) cells, NK T cells, γδ T cells, (ILCs), T cells, or B cells, the method comprising: contacting the lymphocytes obtained from an individual with a composition comprising: i) *Caulobacter crescentus*; and/or ii) an antigen, wherein said contacting is in vitro and wherein said contacting generates a population of regulatory lymphocytes.

23. The method of claim 22, further comprising contacting said regulatory cells with an antigen-presenting cell (APC).

24. The method of claim 22, further comprising administering the regulatory lymphocytes to the individual.

25. A method of regulating an immune response in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of any one of claims 1-8, wherein the number, activity and/or effector functions of a population of regulatory T cells, and/or B cells, and/or NK cells, and/or NKT cells, and/or γδ cells, ILCs, and/or macrophages and/or dendritic cells are modulated.

26. A method of inducing proliferation, differentiation and/or modulation of stem cells and restoration of homeostasis in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of any one of claims 1-8.

27. A method of modifying stem cells, the method comprising contacting the stem cells with a composition comprising *Caulobacter crescentus*, wherein said contacting generates a population of expanded, differentiated and/or modulated stem cells.

28. A method of treating undesirable inflammatory activity, immune dysregulation or an autoimmune disorder in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of any one of claims 1-8.

29. A method of treating a metabolic disorder in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of any one of claims 1-8.

30. A method of treating a neurologic disorder in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of any one of claims 1-8.

31. A method of treating an allergic disease in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of any one of claims 1-8.

32. A method of enhancing the efficacy and/or reducing the toxicity of a therapeutic treatment in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of any one of claims 1-8.

33. A method of treating, restoring or correcting disease- or medical condition-related to imbalances in the microbiome in an individual, the method comprising administering to the individual an effective amount of an immunomodulatory composition of any one of claims 1-8.

Treatment with CC leads to reduction in ConA induced pro-inflammatory cytokine production from splenocytes

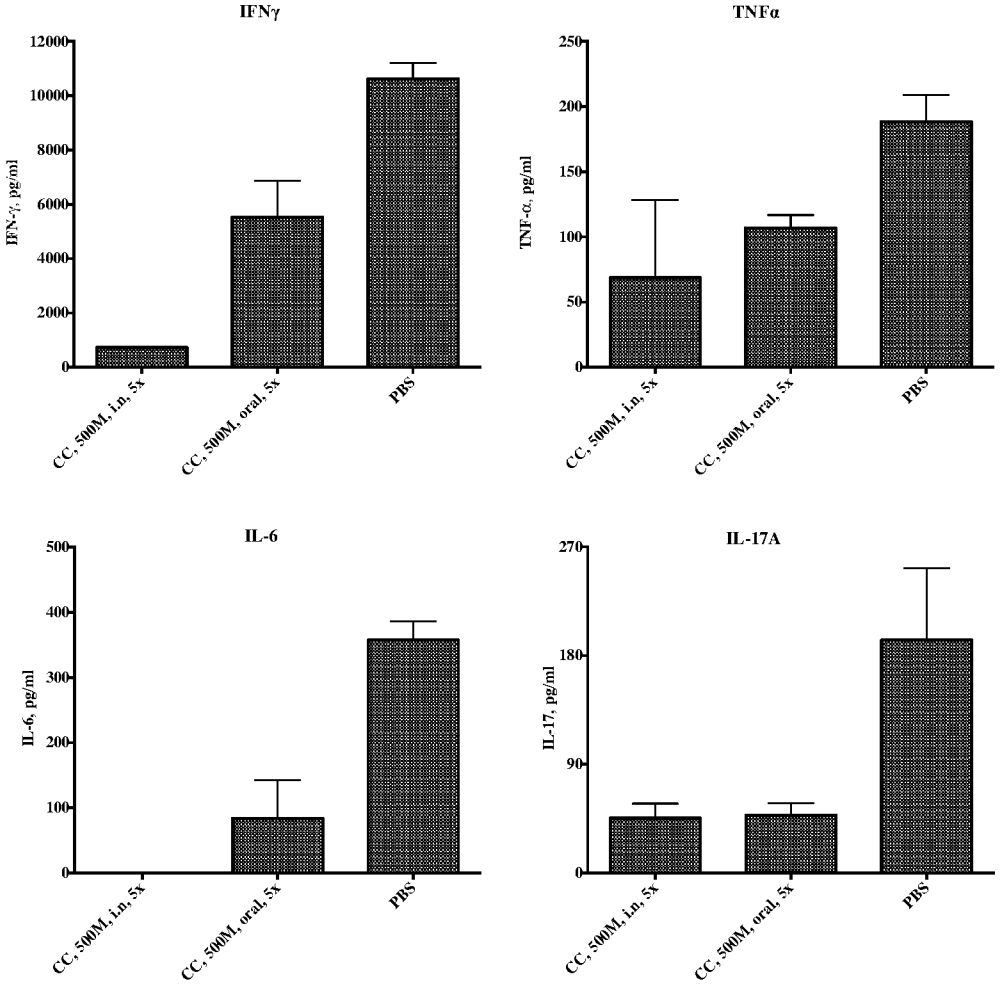


Figure 1

Treatment with CC leads to reduction in PWM induced pro-inflammatory cytokine production from splenocytes

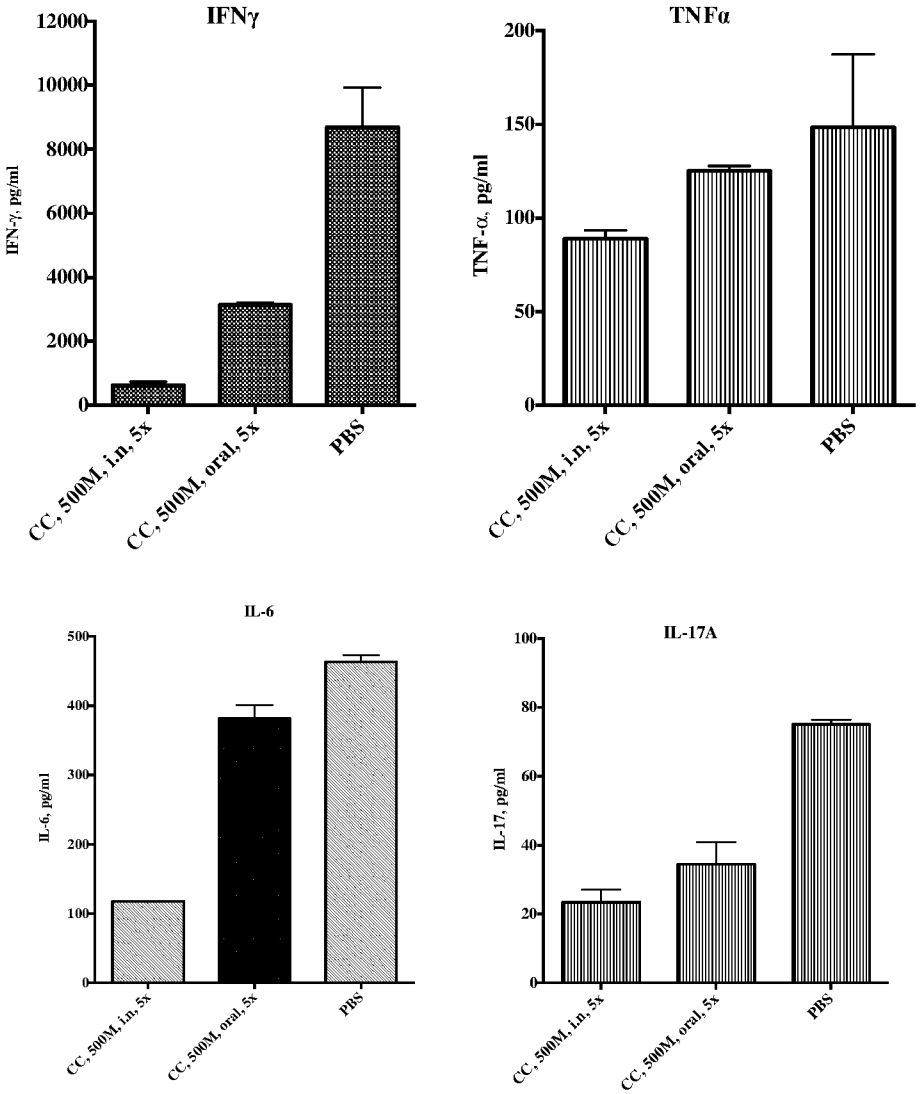


Figure 2

Treatment with CC enhances IL-10 production from splenocytes

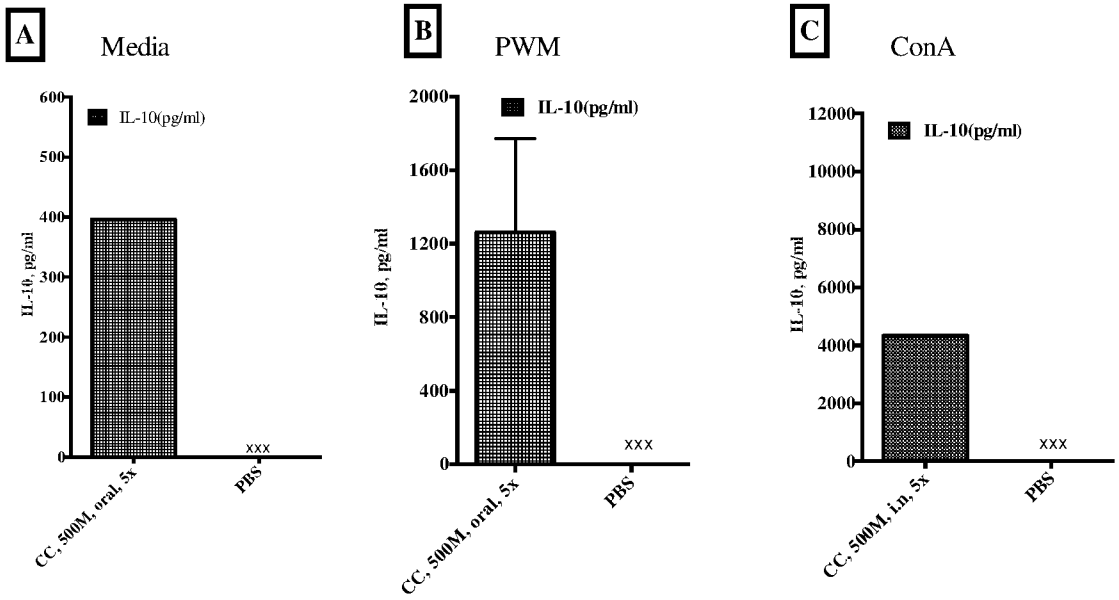


Figure 3

Oral treatment with CC leads to enhanced IL-10 production from LPS-stimulated splenocytes

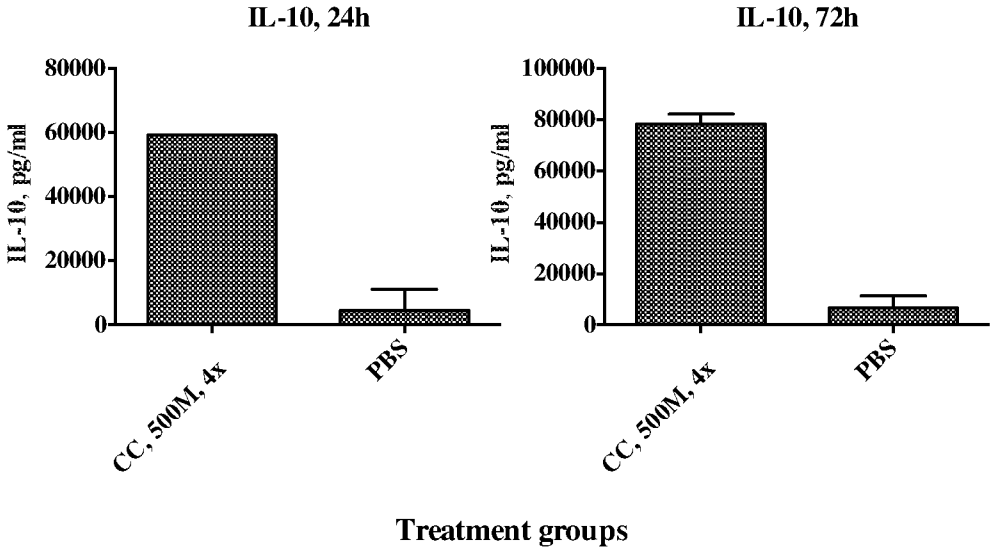


Figure 4

Oral treatment with CC leads to reduced inflammatory cytokine production from LPS-stimulated mesenteric lymph nodes

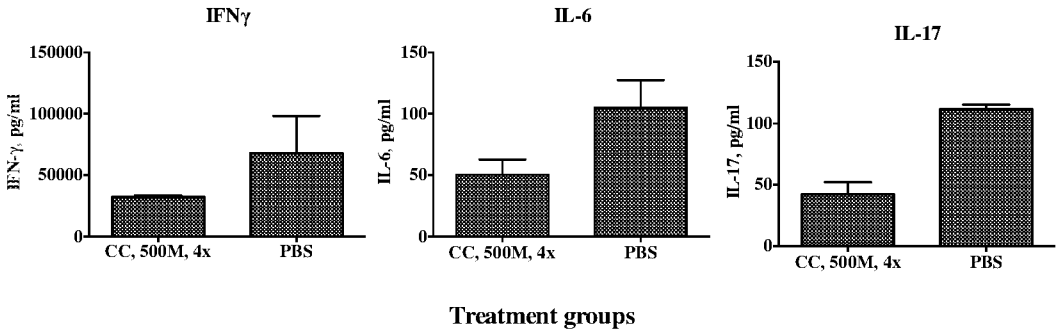


Figure 5

Oral treatment with CC leads to enhancement in IL-10 producing $CD4^+$ and $CD8^+$ T cells in spleen

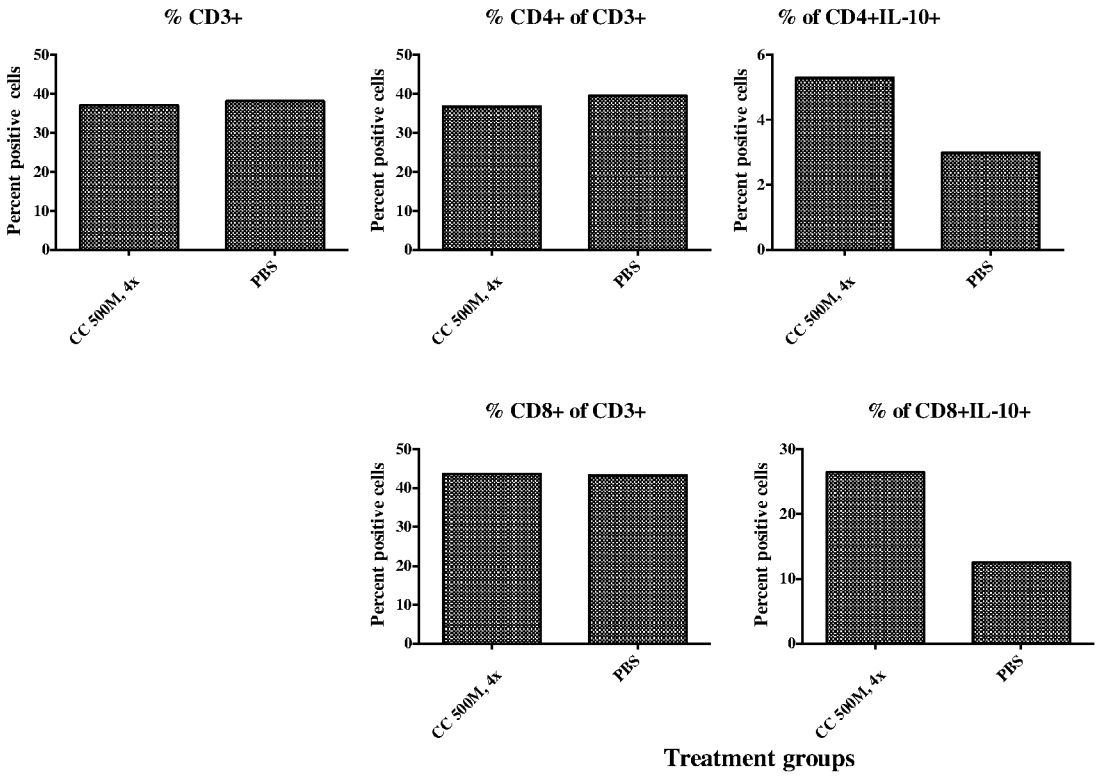


Figure 6

Modulation of pro-inflammatory cytokines in spleen upon subcutaneous treatment with CC

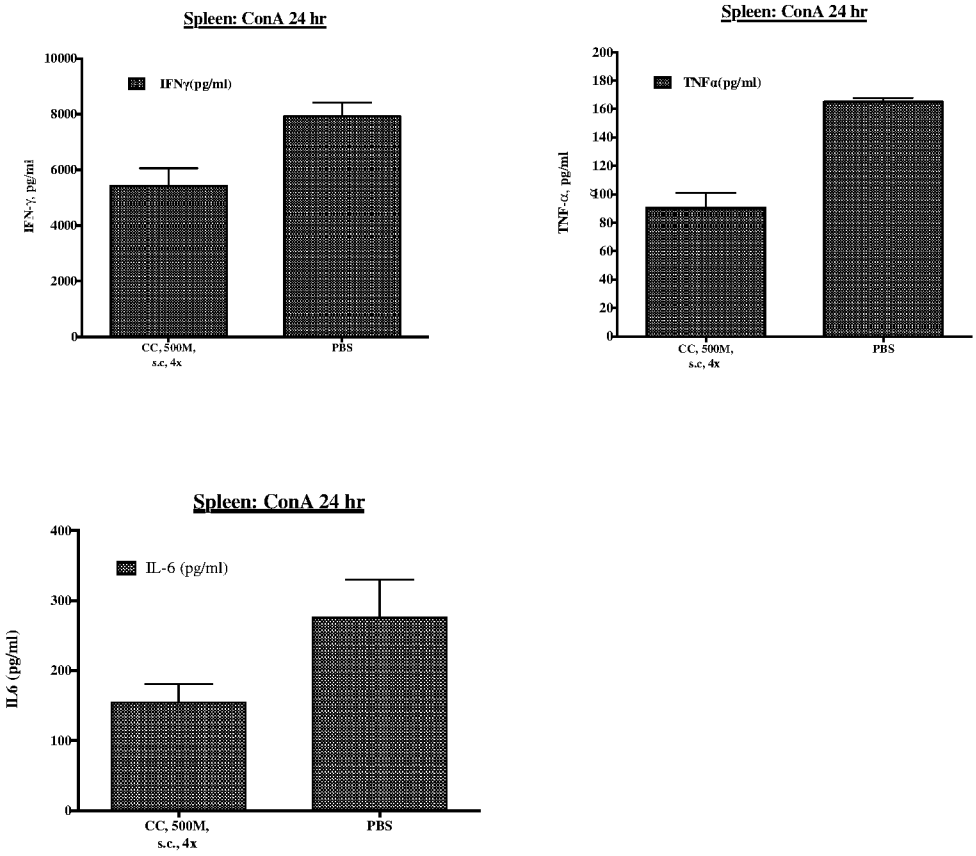


Figure 7

Modulation of immune cells upon oral adminstration of CC

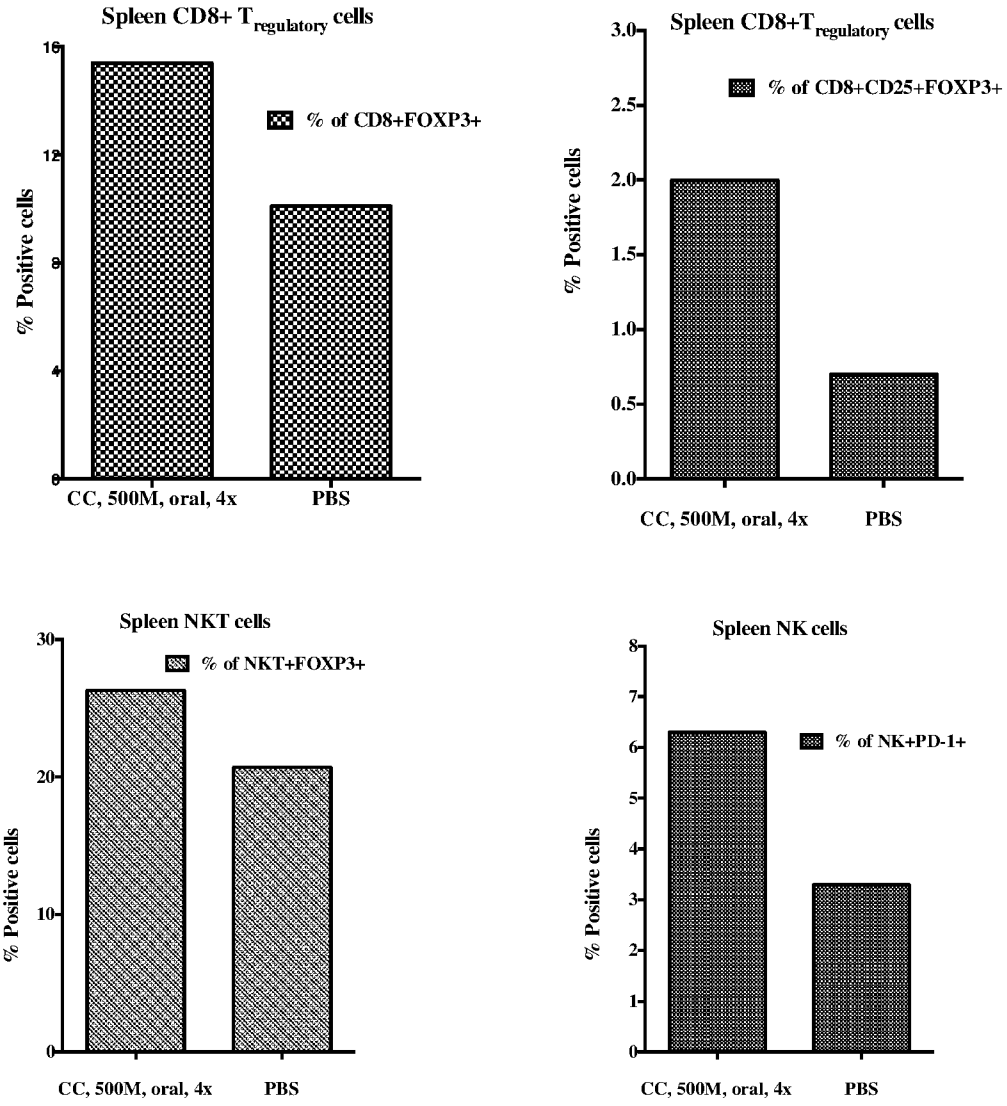


Figure 8

Modulation of immune cells upon subcutaneous administration of CC

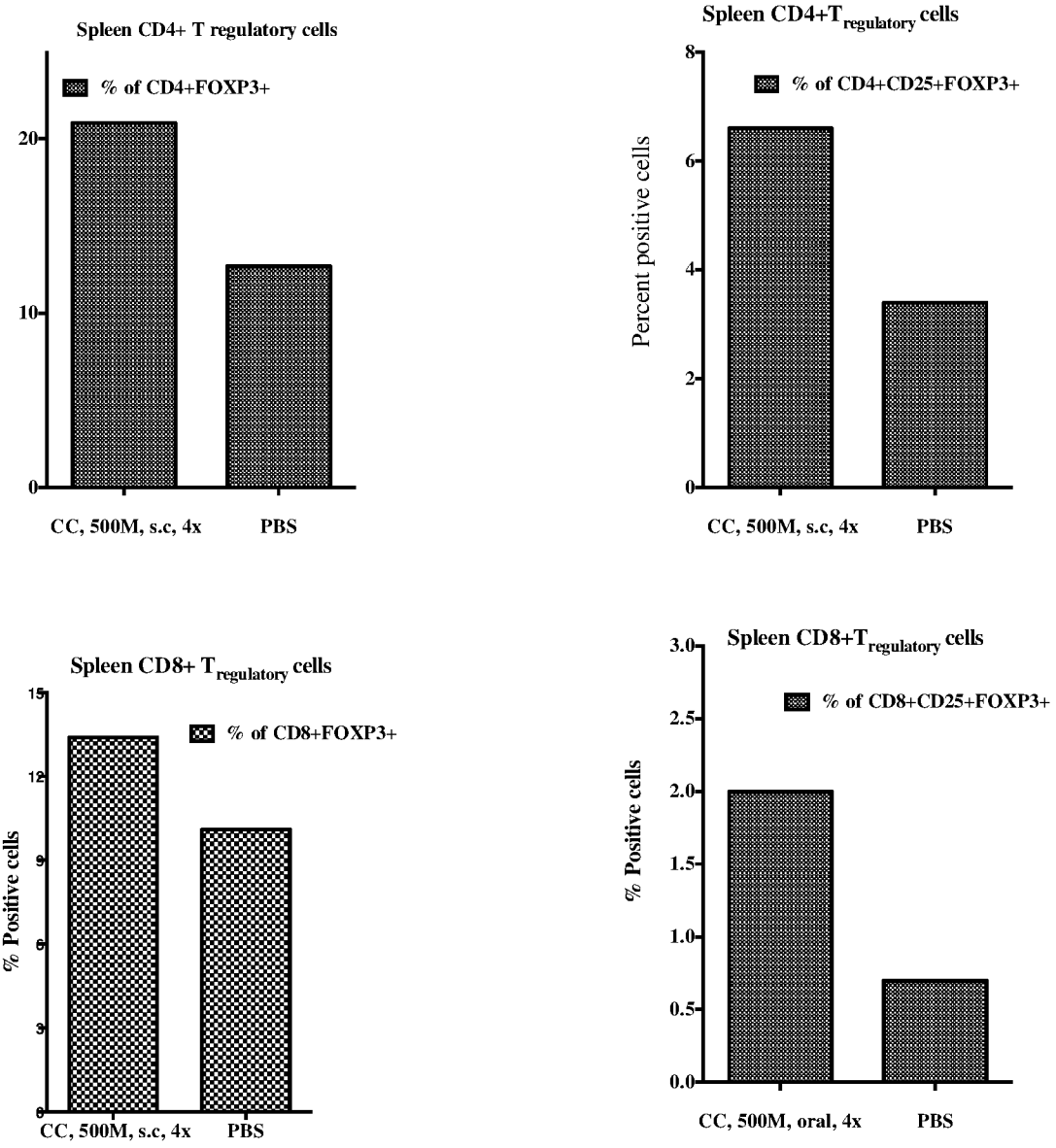


Figure 9

Modulation of serum cytokines by CC in LPS challenged mice

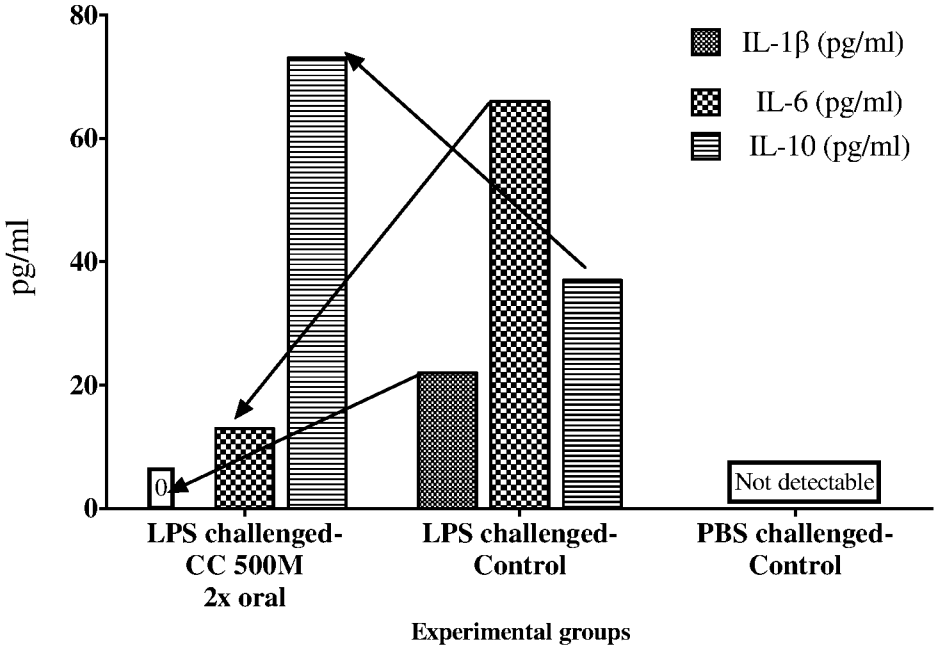


Figure 10

Modulation of cytokines in lungs and liver by CC in LPS challenged mice

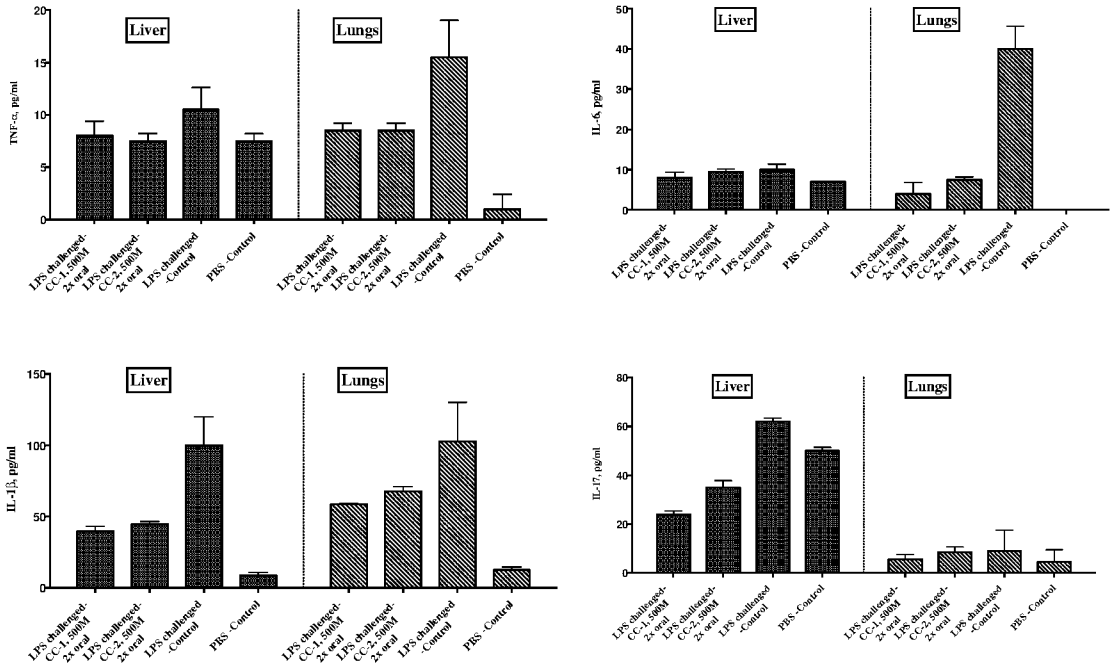


Figure 11

Normalization of serum biochemical markers in CC treated mice-LPS challenge model

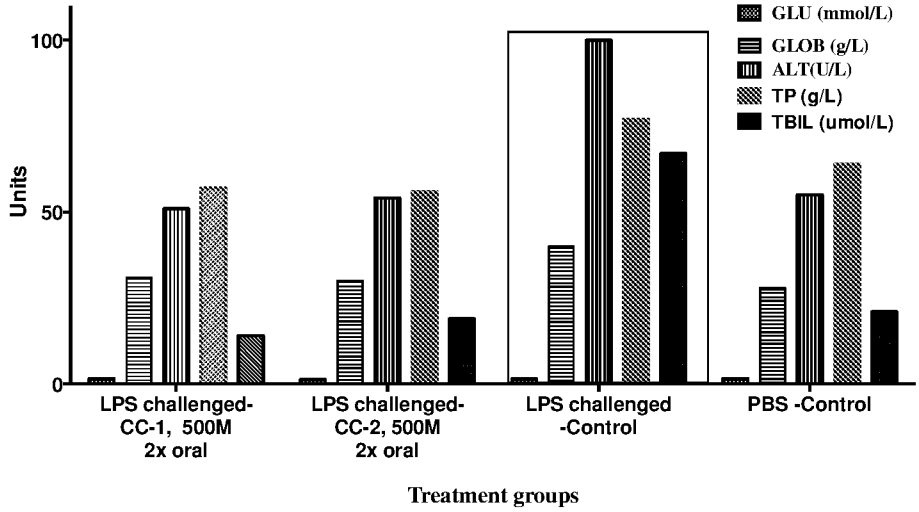
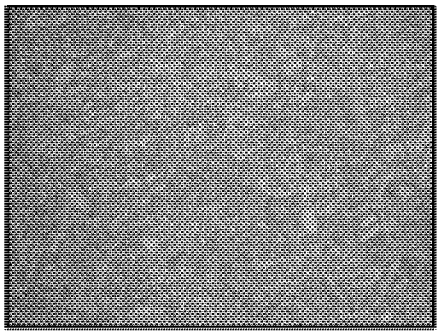
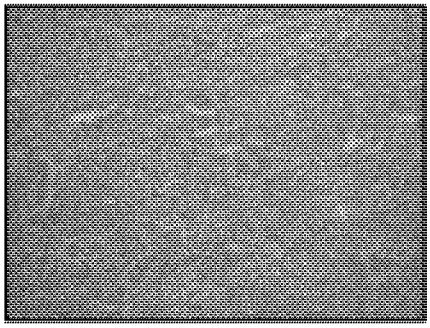


Figure 12

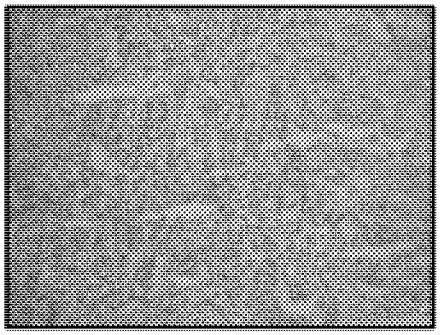
Treatment with CC protects mice from LPS-induced liver damage



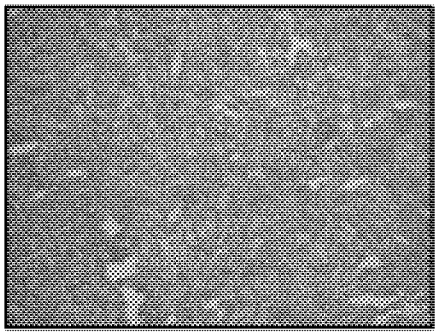
LPS challenged: Treated orally 2x with CC-1



LPS challenged: Treated orally 2x with CC-2



LPS challenged: Control



Normal mouse liver

Figure 13

Modulation of cytokines upon oral treatment with CC in psoriasis afflicted mice

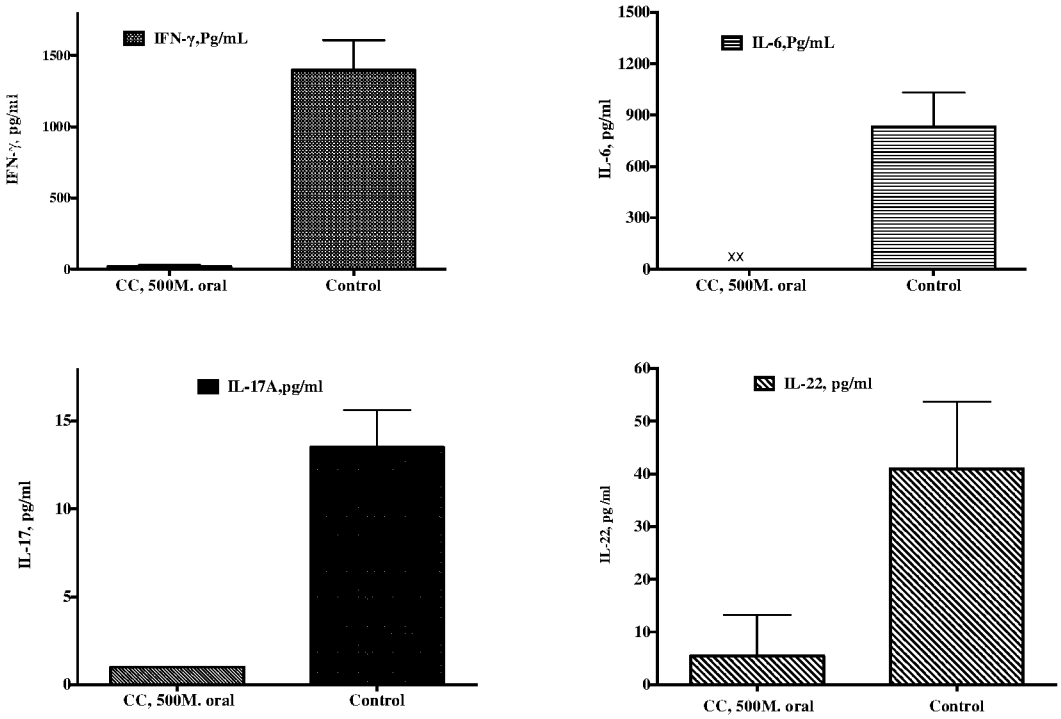


Figure 14

Oral treatment with CC reduces pro-inflammatory cytokines and chemokines in colon tissue of DSS-induced IBD afflicted mice

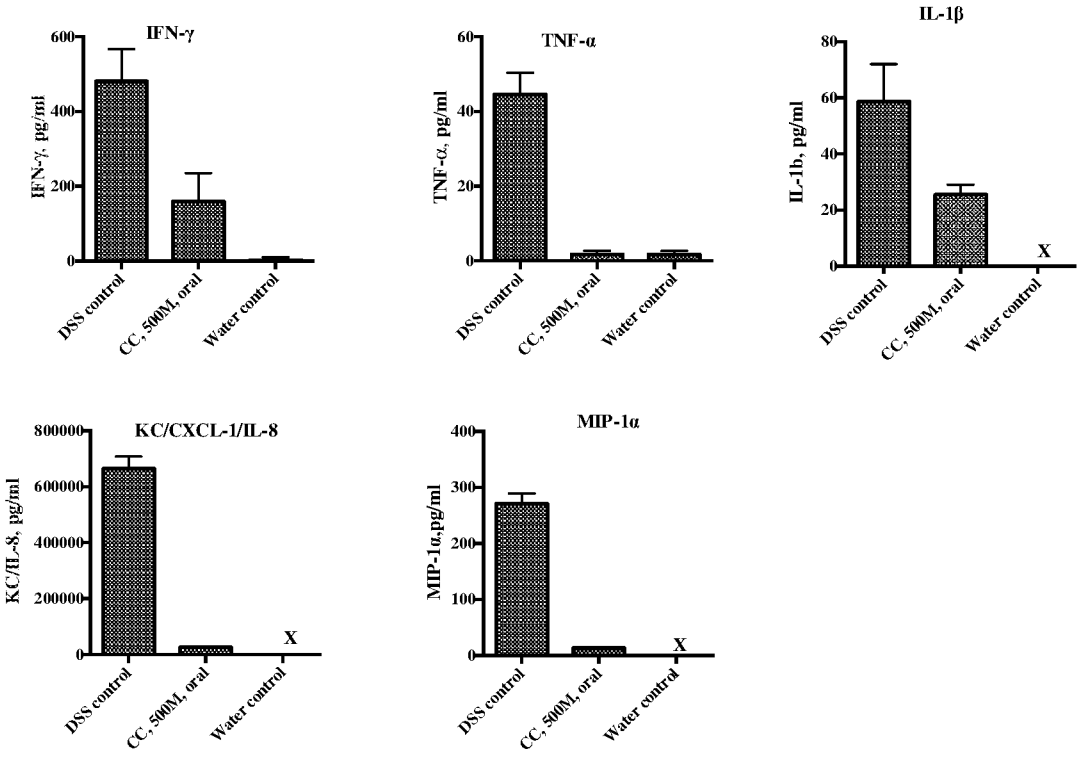


Figure 15

Oral treatment with CC suppresses auto-antigen specific T cell and antibody responses in experimental autoimmune encephalomyelitis (EAE) model

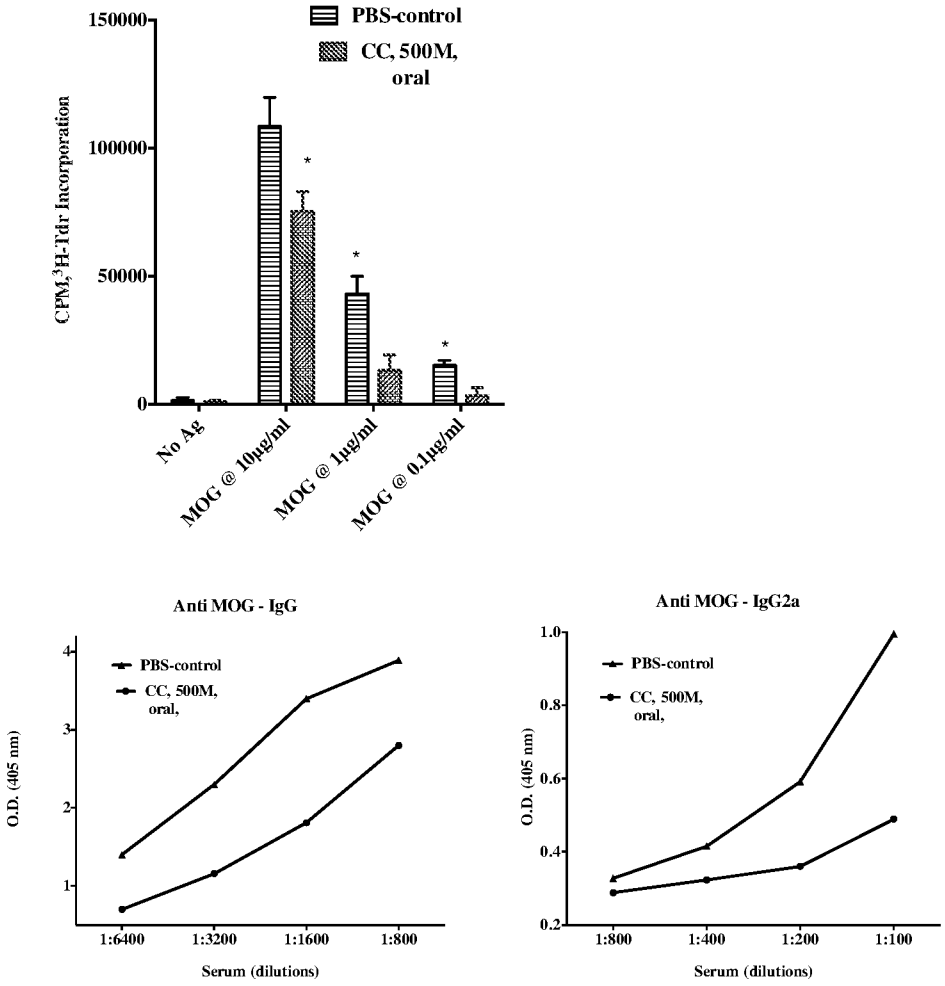


Figure 16

Oral treatment with CC suppresses the levels of allergen (OVA) specific IgE in serum and lung washes in an ovalbumin induced airway inflammation model

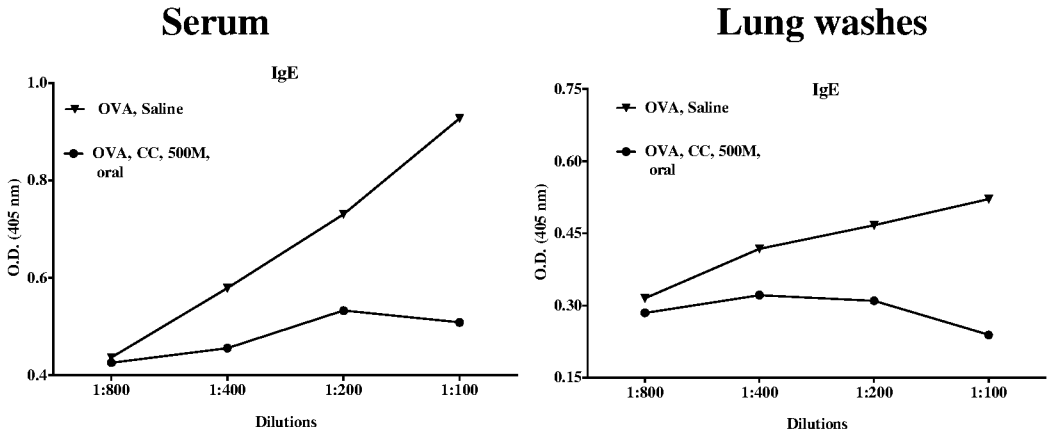


Figure 17

Oral treatment with CC reduces allergen (OVA)-specific cytokines (IL-4 and IL-6) in spleen in murine model

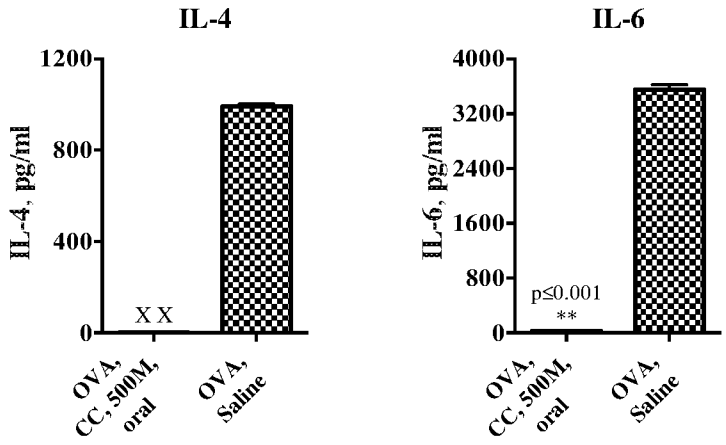


Figure 18

Oral treatment with CC in combination with dexamethasone (DEX) provides enhanced reduction in IL-4 and IL-6 levels in spleen in OVA-induced allergic airway inflammation model, compared to DEX alone

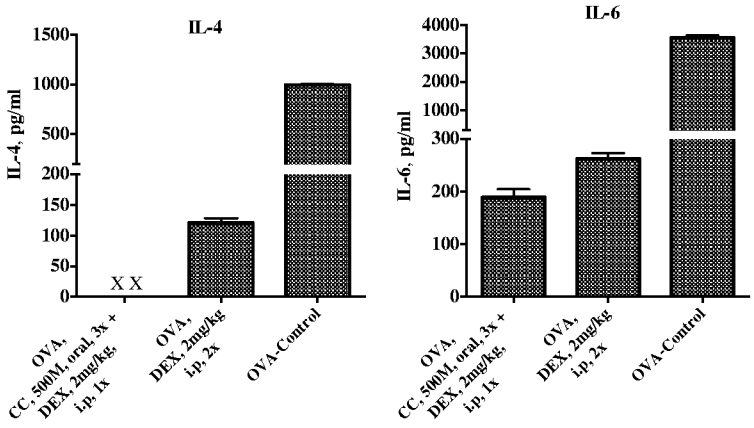


Figure 19

Oral treatment with CC reduces the production of the pro-inflammatory cytokines in liver of high-fat diet fed mice

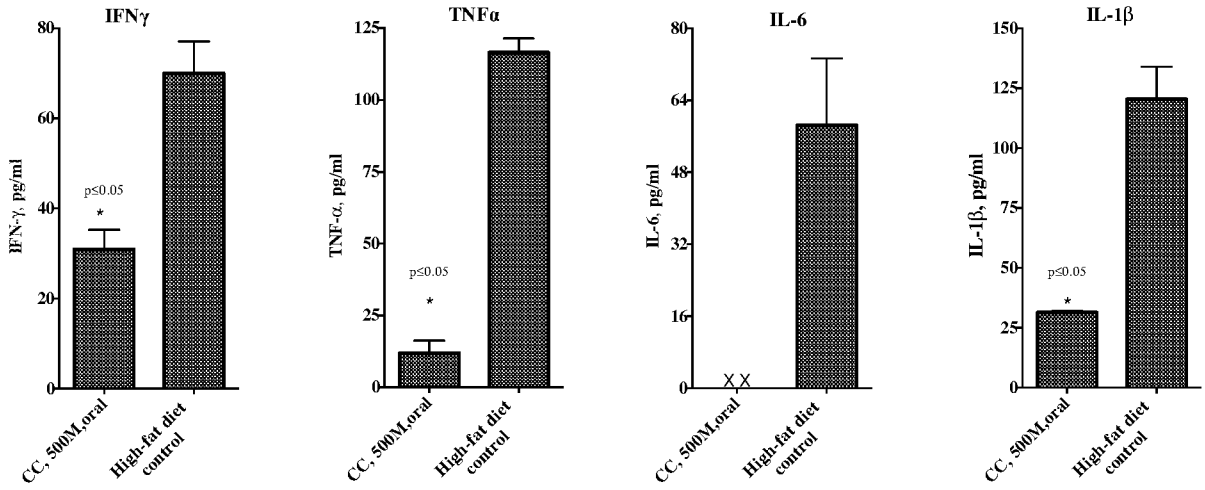


Figure 20

Oral treatment with CC inhibits pro-inflammatory cytokines in spleen of diet-induced obese mice

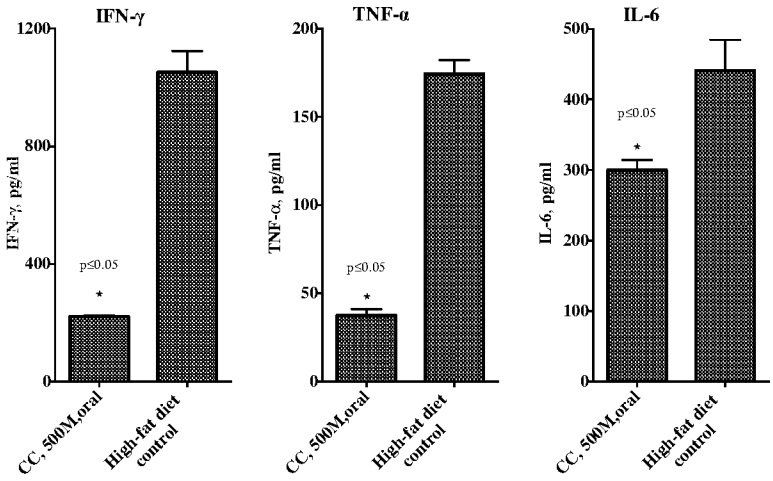


Figure 21

Oral treatment with CC exhibits positive benefits on serum biochemical markers of metabolic diseases in diet-induced obesity model

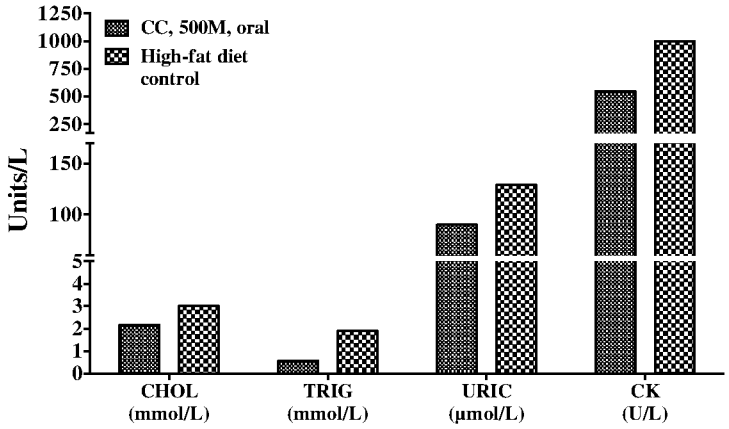


Figure 22

Oral treatment with CC improves glucose tolerance in high-fat diet fed mice

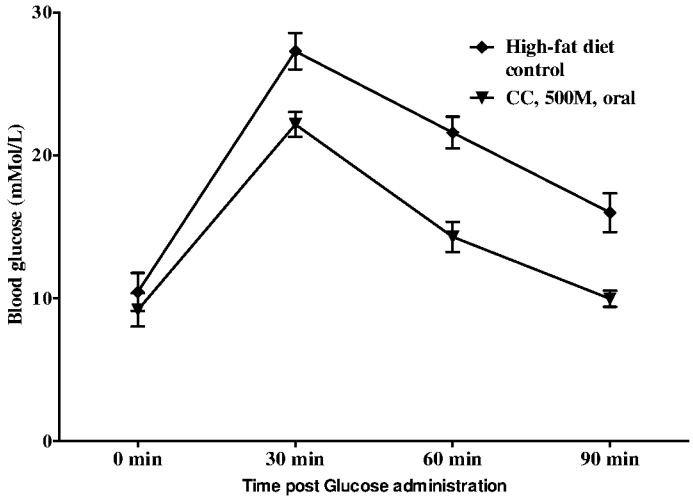


Figure 23

Oral treatment with CC reduces cyclophosphamide associated nephro- and hepato-toxicities in EL-4 lymphoma-bearing C57bl/6 mice

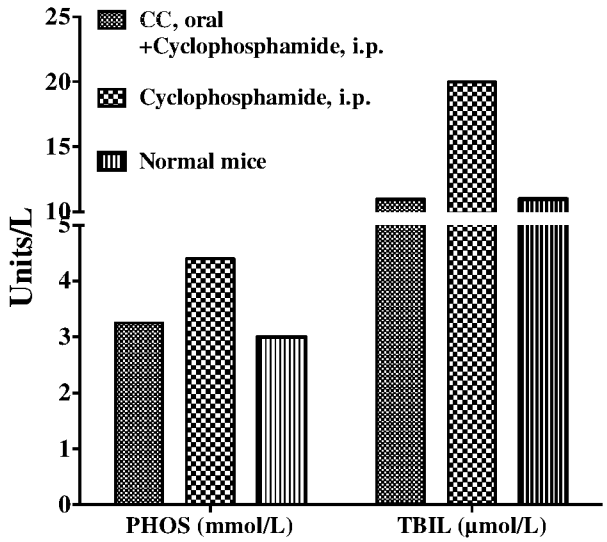


Figure 24

Oral treatment with CC reduces cisplatin associated nephro- and hepato-toxicities in B16 metastatic cancer model

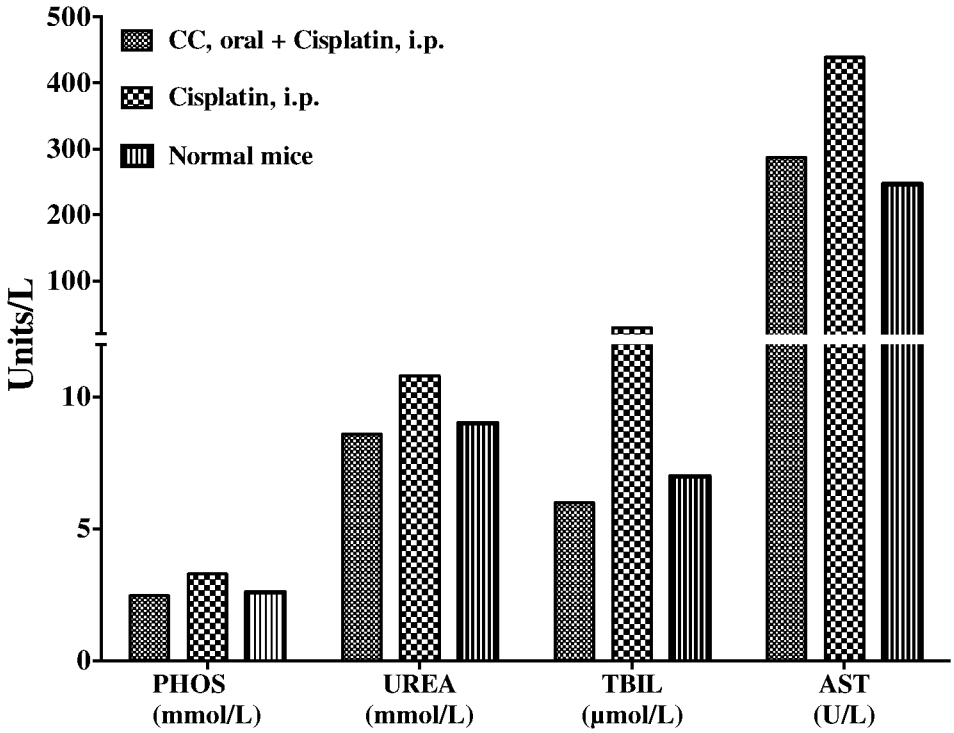


Figure 25

Oral treatment with CC reduces anti-PD1 monoclonal antibody associated hepatotoxicity in B16 tumor bearing C57bl/6 mice

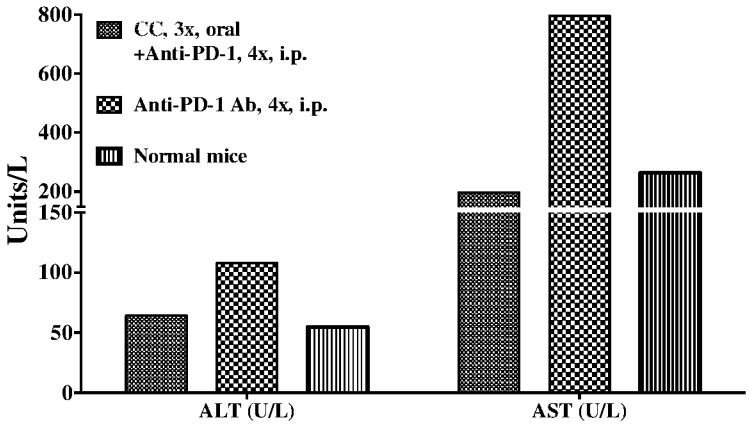


Figure 26

Modulation of cytokines in liver by LPS^{-ve}-CC in mouse model of sepsis

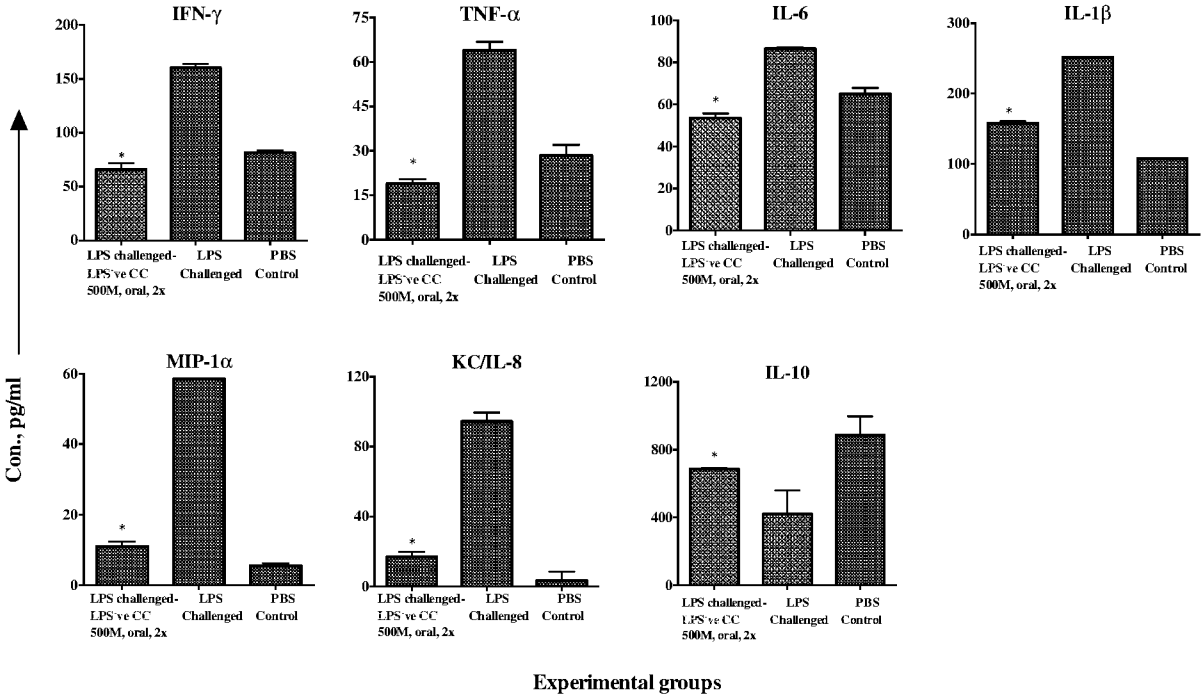


Figure 27

Caulobacter vibroides (CV) reduces pro-inflammatory cytokines induced by a probiotic (*Lactobacillus rhamnosus*) or a pathogenic bacteria (*Lysteria monocytogenes*) in human PBMCs

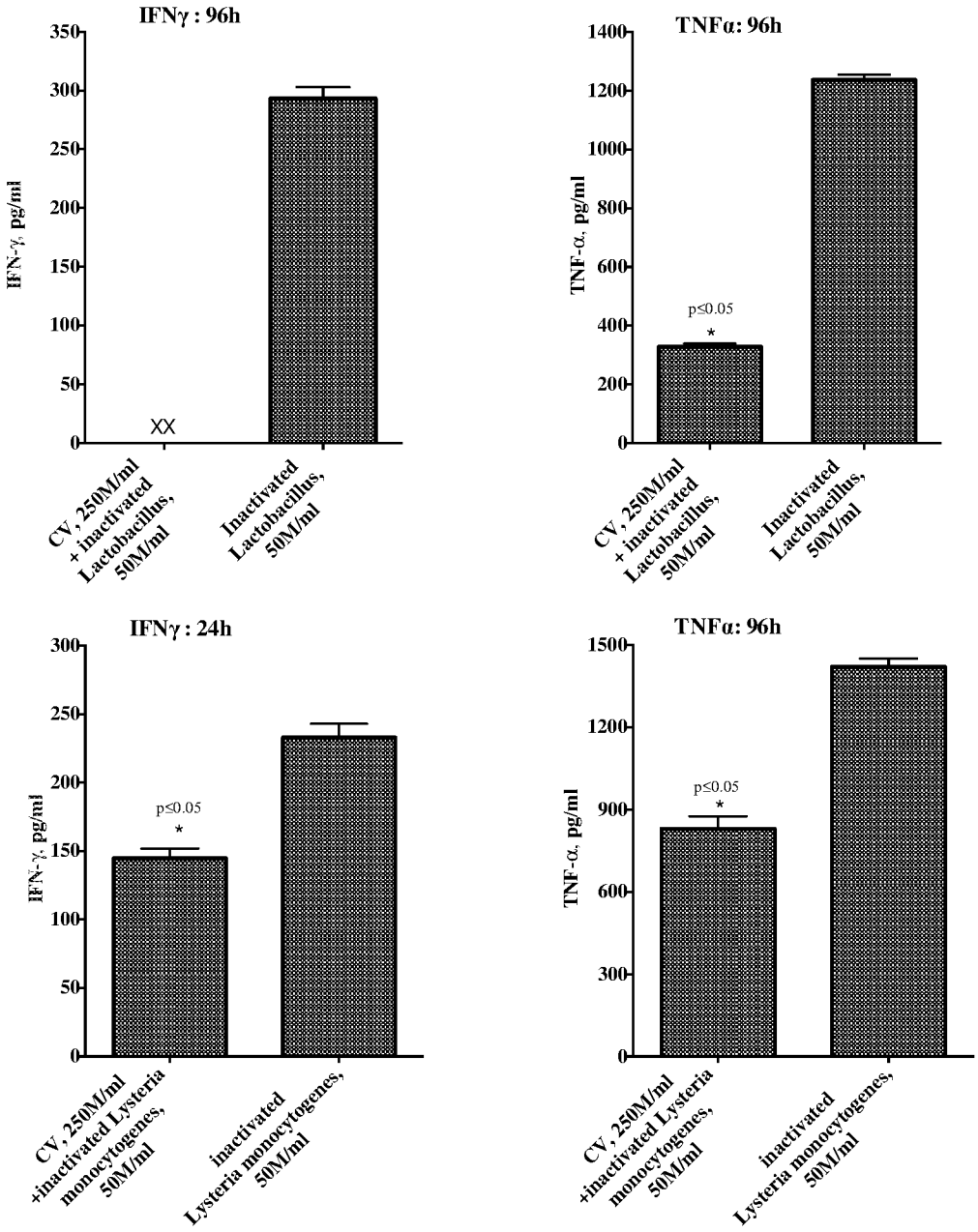


Figure 28

CC modulates human dendritic cells (DCs) *ex vivo*

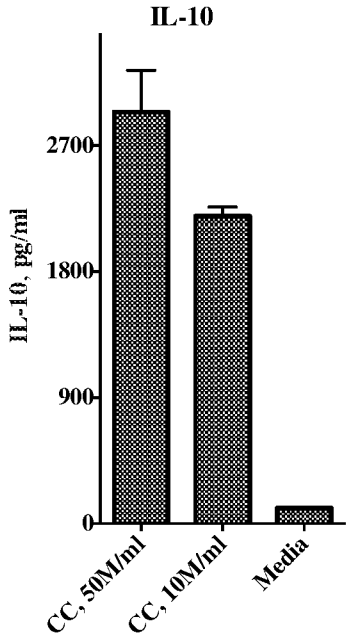


Figure 29

CC leads to differentiation/expansion of pluripotent stem cells (HSC, $CD34^+$) from human PBMCs into myeloid cells

Groups	Total $CD34^+CD45^-$	$CD34^+CD45^-$ $CD11c^+$	$CD34^+CD45^-$ $CD11b^{Á}$
CC, $500x10^6$/ml	1.3	14	11.2
CC, $50x10^6$/ml	1.3	10.7	13.2
CC, $10x10^6$/ml	0.9	7.2	7.2
CC, $1x10^6$/ml	0.9	2	0.7
Saline	0.9	1.2	2

Figure 30

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/055016

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***A61K 39/02*** (2006.01), ***A61K 39/00*** (2006.01), ***A61P 29/00*** (2006.01), ***A61P 3/00*** (2006.01), ***A61P 31/04*** (2006.01), ***A61P 37/02*** (2006.01), ***A61P 37/04*** (2006.01)

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)
A61K 39/02 (2006.01), ***A61K 39/00*** (2006.01), ***A61P 29/00*** (2006.01), ***A61P 3/00*** (2006.01), ***A61P 31/04*** (2006.01), ***A61P 37/02*** (2006.01), ***A61P 37/04*** (2006.01)

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Canadian Patent database, Total Patent, PubMed, Internet (Google), Scopus

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	CA2935511 A1 (AGRAWAL, B. et al.) 16 July 2015 (16-07-2015)	1-8 20-23

☐ Further documents are listed in the continuation of Box C.

☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 November 2016 (16-11-2016)	18 November 2016 (18-11-2016)

Name and mailing address of the ISA/CA	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 819-953-2476	Damiano Conte (819) 639-7784

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/055016

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claim Nos.: 9-19 and 24-33
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 9-19 and 24-33 are directed to a method for treatment of the human or animal body by surgery or therapy, which the International Searching Authority is not required to examine under PCT Rule 67.1(iv). However, this Authority has established a written opinion based on the alleged use of a composition consisting of a live Caulobacter crescentus and a pharmaceutical excipient.

2. ☑ Claim Nos.: 20-24 (all partially)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 20-24 encompass a product with insufficient technical features. The application provides adequate disclosure within the meaning of Article 5 for specifically only dendritic cells contacted with any of live Caulobacter crescentus or live Caulobacter crescentus and an antigen. In the present case, the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been established for the parts of the application which appear to be clear and/or supported, namely dendritic cells contacted with any of live Caulobacter crescentus or live Caulobacter crescentus and an antigen and not to an antigen alone.

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2016/055016

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
CA2935511 A1	16 July 2015 (16-07-2015)	WO2015104656	16 July 2015 (16-07-2015)
		AU2015205342	21 July 2016 (21-07-2016)
		US2016317637	3 November 2016 (03-11-2016)

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A61P 3/00(2006.01)
A61P 31/04(2006.01)
A61P 37/02(2006.01)
A61P 37/04(2006.01)

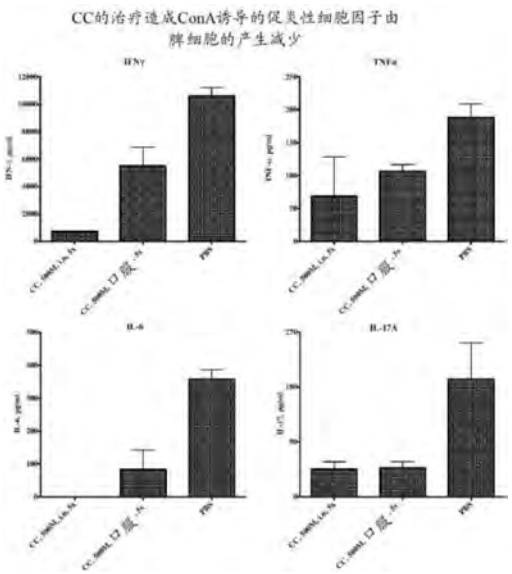
权利要求书2页 说明书78页 附图21页

(54)发明名称

免疫调节组合物及其使用方法

(57)摘要

本公开提供包含活的新月柄杆菌(CC)的免疫调节组合物。本公开的免疫调节组合物可用于调节个体中的免疫应答。本公开因此提供调节个体中的免疫应答的方法,所述方法涉及向所述个体施用包含活CC的免疫调节组合物。



CN 107921113 A

1.一种免疫调节组合物,其包含:

a)活的新月柄杆菌;和

b)药学上可接受的赋形剂。

2.如权利要求1所述的组合物,其还包含抗原、自身抗原或过敏原。

3.如权利要求1或权利要求2所述的组合物,其中所述新月柄杆菌为野生型、脂多糖阴性菌株或S层阴性菌株。

4.如权利要求1-3中任一项所述的组合物,其中所述新月柄杆菌为活的、非变性的、突变的、减毒的或遗传修饰的。

5.如权利要求1-3中任一项所述的组合物,其中所述新月柄杆菌被遗传修饰以产生一种或多种异源多肽,其中异源多肽选自自身抗原、过敏原、细胞因子、共刺激或共抑制分子、趋化因子、免疫球蛋白或其抗原结合片段、抗微生物剂。

6.如权利要求1-5中任一项所述的组合物,其还包含治疗性抗体。

7.如权利要求1-6中任一项所述的组合物,其还包含益生菌病原体、共生菌病原体、治疗性病原体、或来自患者的微生物组的治疗性细菌。

8.如权利要求1-6中任一项所述的组合物,其还包含至少一种佐剂、细胞因子或选自以下的治疗剂:抗炎剂、抗增殖剂、细胞毒性剂、免疫抑制剂、免疫调控剂、免疫调节剂、抗组胺剂或抗微生物剂。

9.一种调节个体中的免疫应答的方法,所述方法包括向所述个体施用有效量的如权利要求1-8中任一项所述的免疫调节组合物。

10.如权利要求9所述的方法,其中所述免疫应答包括调节一种或多种细胞因子。

11.如权利要求9所述的方法,其中所述免疫应答为体液免疫应答、细胞免疫应答或先天性免疫应答。

12.如权利要求9所述的方法,其还包括向所述个体施用自身抗原或过敏原。

13.如权利要求9所述的方法,其还包括向所述个体施用治疗性治疗,如放射疗法、激光疗法、光动力疗法和/或手术。

14.如权利要求9所述的方法,其还包括向所述个体施用抗细菌剂、抗分枝杆菌剂、抗原生动物剂、抗疟疾剂、抗蠕虫剂、抗病毒剂、抗组胺剂、抗糖尿病剂、抗炎剂、抗增殖剂、细胞毒性剂、免疫抑制剂或免疫调节剂。

15.如权利要求9所述的方法,其还包括向所述个体施用抗体。

16.如权利要求9所述的方法,其还包括向所述个体施用细胞因子、佐剂或免疫调控剂。

17.如权利要求9所述的方法,其还包括向所述个体施用益生菌、共生菌、来自微生物组的治疗性成员或治疗性病原体。

18.如权利要求9-17中任一项所述的方法,其中所述个体为人、非人哺乳动物或非哺乳动物的动物。

19.如权利要求9-18中任一项所述的方法,其中所述组合物是经由口、鼻、皮下、肌内、静脉内、阴道、经皮、局部、直肠、眼或粘膜施用途径来施用。

20.一种调节树突细胞的方法,所述方法包括:

a)使从个体处获得的树突细胞(DC)与包含以下的组合物接触:i)新月柄杆菌;和/或ii)抗原,其中所述接触是在体外且其中所述接触调节所述DC上的抗原呈递,由此产生调节

的DC群。

21.如权利要求20所述的方法,其还包括向所述个体施用所述调节的DC。

22.一种产生调控性淋巴细胞的方法,其中所述调控性淋巴细胞为天然杀伤(NK)细胞、NK T细胞、γδT细胞(ILC)、T细胞或B细胞,所述方法包括:使从个体获得的淋巴细胞与包含以下的组合物接触:i)新月柄杆菌;和/或ii)抗原,其中所述接触是在体外且其中所述接触产生调控性淋巴细胞群。

23.如权利要求22所述的方法,其还包括使所述调控性细胞与抗原呈递细胞(APC)接触。

24.如权利要求22所述的方法,其还包括向所述个体施用所述调控性淋巴细胞。

25.一种调控个体中的免疫应答的方法,所述方法包括向所述个体施用有效量的如权利要求1-8中任一项所述的免疫调节组合物,其中调节性T细胞和/或B细胞和/或NK细胞和/或NKT细胞和/或γδ细胞、ILC和/或巨噬细胞和/或树突细胞群的数量、活性和/或效应子功能受到调节。

26.一种诱导个体中的干细胞的增殖、分化和/或调节及恢复体内平衡的方法,所述方法包括向所述个体施用有效量的如权利要求1-8中任一项所述的免疫调节组合物。

27.一种修饰干细胞的方法,所述方法包括使所述干细胞与包含新月柄杆菌的组合物接触,其中所述接触产生扩增的、分化的和/或调节的干细胞群。

28.一种治疗个体中的不希望的炎性活性、免疫失调或自身免疫病症的方法,所述方法包括向所述个体施用有效量的如权利要求1-8中任一项所述的免疫调节组合物。

29.一种治疗个体中的代谢病症的方法,所述方法包括向所述个体施用有效量的如权利要求1-8中任一项所述的免疫调节组合物。

30.一种治疗个体中的神经病症的方法,所述方法包括向所述个体施用有效量的如权利要求1-8中任一项所述的免疫调节组合物。

31.一种治疗个体中的过敏性疾病的方法,所述方法包括向所述个体施用有效量的如权利要求1-8中任一项所述的免疫调节组合物。

32.一种提高个体中的治疗性治疗的功效和/或降低其毒性的方法,所述方法包括向所述个体施用有效量的如权利要求1-8中任一项所述的免疫调节组合物。

33.一种治疗、恢复或纠正与个体中的微生物组失衡有关的疾病或医学病状的方法,所述方法包括向所述个体施用有效量的如权利要求1-8中任一项所述的免疫调节组合物。

免疫调节组合物及其使用方法

[0001] 引言

[0002] 新月柄杆菌(Caulobacter crescentus)为非病原的、无害的、水生革兰氏阴性细菌,其生长在～23℃的许多土壤和淡水环境中。已对柄杆菌属研究了近50年。主要实验室菌株(新月柄杆菌CB15)已在遗传和生物化学上得到充分表征,并且已对新月柄杆菌的基因组进行测序。柄杆菌属容易使用标准实验室设备进行生长。它们还容易在商用的发酵罐中在无动物蛋白的限定基本培养基中生长至至少30个光密度单位(OD)。

[0003] 在本领域中需要免疫调节组合物,其可用于预防和/或治疗以下病症:如炎症、不希望的炎性活性、加剧的免疫应答、异常的免疫应答、免疫失调及自身免疫疾病。

[0004] 概述

[0005] 本公开提供包含新月柄杆菌(CC)的免疫调节组合物。本公开的免疫调节组合物可用于调节个体中的免疫应答。本公开提供调节个体中的免疫应答的方法,所述方法涉及向所述个体施用包含CC的免疫调节组合物。

[0006] 附图简述

[0007] 图1示出了在从用CC和PBS每周两次经由鼻内和口服途径处理的小鼠中分离的脾细胞中伴刀豆球蛋白A(ConA)诱导的促炎性细胞因子(IFN-γ、TNF-α、IL-6及IL-17A)产生的减少。数据用pg/ml表示并且显示为一式三份的平均值+标准偏差(SD)。

[0008] 图2示出了在从用CC和磷酸盐缓冲盐水(PBS)每周两次经由鼻内和口服途径处理的小鼠中分离的脾细胞中的美洲商陆有丝分裂原(PWM)诱导的促炎性细胞因子(IFN-γ、TNF-α、IL-6及IL-17A)产生的减少。数据用pg/ml表示并且显示为一式三份的平均值+SD。

[0009] 图3A-3C示出了在从用CC和PBS每周两次经由鼻内和口服途径处理并用培养基(A)、PWM(B)及ConA(C)离体刺激24h的小鼠中分离的脾细胞中的IL-10的诱导。数据用pg/ml表示并且显示为一式三份的平均值+SD。

[0010] 图4示出了在从用CC和PBS每周两次经口处理的小鼠中分离的脾细胞中IL-10的诱导分布。用LPS体外刺激细胞24小时或72小时。

[0011] 图5示出了在从用CC和PBS每周两次经口施用的小鼠中分离的肠系膜淋巴结中细胞因子(IFN-γ、IL-6及IL-17A)的分布减少。用脂多糖(LPS)体外刺激细胞24小时。数据显示为平均值+SD。

[0012] 图6示出了在从每周两次喂予CC和PBS的小鼠中分离的脾细胞中产生IL-10的CD4+和CD8+T细胞的增强。呈现表达细胞内IL-10且对CD3和CD4或CD8呈阳性的细胞百分比。

[0013] 图7示出了在从用CC和PBS每周一次经由皮下途径处理的小鼠中分离的脾细胞中ConA诱导的促炎性细胞因子(IFN-γ、TNF-α及IL-6)产生的调节。数据用pg/ml表示并且显示为一式三份的平均值+SD。

[0014] 图8示出了在用CC或PBS每周一次经口处理的小鼠中调控性淋巴细胞(CD8T细胞、NKT细胞及NK细胞)的诱导。数据代表表达CD25、FoxP3或PD-1的$CD3^{+}CD8^{+}$、CD3+CD49b+及$CD3^{-}CD49b^{+}$群。

[0015] 图9示出了在用CC或PBS每周一次皮下处理的小鼠中调控性淋巴细胞(CD4和CD8T

细胞)的诱导。数据代表表达CD25和FoxP3的$CD3^+CD4^+$和$CD3^+CD8^+$群。

[0016] 图10示出了在来自用7mg/Kg的LPS体内激发后2小时(hrs)用CC和PBS经口处理的小鼠的血清样品中IL-1β、IL-6及IL-10的调节。LPS激发的小鼠在血清中的炎性细胞因子有显著增加,这在用CC处理的小鼠中是减少的。相比之下,CC处理造成LPS激发的小鼠中IL-10的增加。

[0017] 图11示出了在来自用7mg/Kg的LPS体内激发2h后用CC和PBS经口处理的小鼠的肝脏和肺脏匀浆样品中TNF-α、IL-6、IL-1β及IL-17A的调节。将所用的CC以两种形式制备:CC-1(在液体胨酵母提取物(PYE)培养基中生长且在室温下在盐水中储存的CC),和CC-2(在液体PYE培养基中生长且在4℃下冰箱中储存的CC)。数据表示为三个孔的平均值+SD。

[0018] 图12示出了在来自用7mg/Kg的LPS体内激发2h后用CC和PBS经口处理的小鼠的血清样品中的生化参数(GLU:葡萄糖;GLOB:球蛋白;ALT:丙氨酸转氨酶;TP:总磷酸盐;TBIL:总胆红素)。将所用的CC以两种形式制备:CC-1(在液体PYE培养基中生长且在室温下在盐水中储存的CC),和CC-2(在液体PYE培养基中生长且在4℃下冰箱中储存的CC)。

[0019] 图13示出了从用7mg/Kg的LPS体内激发2h后用CC和PBS经口处理的小鼠中分离的肝脏切片的苏木精和曙红(H&E)染色。将所用的CC以两种形式制备:CC-1(在液体PYE培养基中生长且在室温下在盐水中储存的CC),和CC-2(在液体PYE培养基中生长且在4℃下冰箱中储存的CC)。

[0020] 图14示出了在Aldra(咪喹莫特)诱导的牛皮癣小鼠模型中用CC和PBS经口处理两周(5天/周)后的细胞因子(IFN-γ、IL-6、IL-17A及IL-22)的调节。从小鼠中收获脾细胞并在培养基中离体培养4天,然后收集上清液并测试细胞因子。

[0021] 图15示出了在DSS(葡聚糖硫酸钠)诱导的IBD(炎性肠病)小鼠模型中细胞因子(IFN-γ、TNF-α、IL-1β、IL-8、MIP-1α)的调节。数据用pg/ml表示并且显示为一式三份的平均值+SD。

[0022] 图16示出了在实验性自身免疫性脑脊髓炎(EAE)小鼠模型中用CC经口处理之后的自身抗原特异性T细胞增殖及抗体(IgG和IgG2a)应答的抑制。

[0023] 图17示出了在卵清蛋白诱导的过敏性气道炎症模型中用CC经口处理后的过敏原特异性IgE抗体应答的抑制。

[0024] 图18示出了在卵清蛋白诱导的过敏性气道炎症模型中用CC经口处理后在脾脏中的过敏原特异性细胞因子(IL-4和IL-6)的减少。数据用pg/ml表示并且显示为一式三份的平均值+SD。

[0025] 图19示出了在卵清蛋白诱导的过敏性气道炎症模型中用CC+地塞米松(DEX)、DEX单独经口处理或无处理对照后在脾脏中的过敏原特异性细胞因子(IL-4和IL-6)的减少。数据用pg/ml表示并且显示为一式三份的平均值+SD。

[0026] 图20示出了与未处理的高脂饮食饲喂的小鼠相比用CC的经口处理对高脂饮食的小鼠的肝脏中的促炎性细胞因子(IFN-γ、TNF-α、IL-6及IL-1β)的作用。在开始高脂饮食之后～180天获取数据并显示为5只小鼠的平均值+SD。数据用pg/ml表示并且显示为一式三份的平均值+SD。

[0027] 图21示出了与未处理的高脂饮食饲喂的小鼠相比用CC的经口处理对高脂饮食的小鼠的脾脏中的促炎性细胞因子(IFN-γ、TNF-α及IL-6)的作用。在开始高脂饮食之后～

180天获取数据并显示为5只小鼠的平均值+SD。数据用pg/ml表示。

[0028] 图22示出了在来自高脂饮食的经CC处理的小鼠的血清样品中的生化参数(CHOL:胆固醇;TRIG:甘油三酯;URIC:尿酸;CK:肌酸激酶),并且与未处理的高脂饮食饲喂的小鼠相比。在开始高脂饮食之后～180天获取数据并显示为5只小鼠的平均值。

[0029] 图23示出了与未处理的高脂饮食饲喂的小鼠相比CC在高脂饮食的小鼠中对葡萄糖耐受性的影响。在开始高脂饮食之后～180天获取数据并显示为5只小鼠的平均值+SD。

[0030] 图24示出了在来自携带EL-4皮下肿瘤的经CC+环磷酰胺和环磷酰胺处理的小鼠的血清样品中的生化参数(PHOS:磷酸盐;TBIL:总胆红素),并且与正常小鼠相比。

[0031] 图25示出了在来自患有B16转移性癌症的经CC+顺铂和顺铂处理的小鼠的血清样品中的生化参数(PHOS:磷酸盐;UREA;TBIL:总胆红素;AST:天冬氨酸转氨酶),并且与正常小鼠相比。

[0032] 图26示出了在来自患有B16肿瘤的经CC+抗PD-1单克隆抗体和抗PD-1单克隆抗体处理的小鼠的血清样品中的生化参数(ALT:丙氨酸转氨酶;AST:天冬氨酸转氨酶),并且与正常小鼠相比。

[0033] 图27示出了在来自用25mg/Kg,i.p LPS体内激发2和24h后用LPS^{-ve} CC和PBS经口处理的小鼠的肝脏匀浆样品中IFN-γ、TNF-α、IL-6、IL-1β、MIP-1α、IL-8及IL-10的调节。数据用pg/ml表示并且显示为三个孔的平均值+SD。

[0034] 图28显示弧形柄杆菌(CV)可造成在人PBMC细胞培养物中由益生菌(鼠李糖乳杆菌(Lactobacillus rhamnosus),LB)或致病细菌(单核细胞增多性李斯特氏菌(Lysteria monocytogenes),LM)诱导的炎性细胞因子(IFN-γ和TNF-α)的下调。数据用pg/ml表示并且显示为三个孔的平均值+SD。

[0035] 图29示出了CC诱导离体培养的人髓样树突细胞(DC)产生IL-10。数据用pg/ml表示并且显示为三个孔的平均值+SD。

[0036] 图30显示CC可用于从存在于人外周血液中的多能干细胞分化/扩增髓性细胞。数据代表如通过流式细胞术所测定的$CD34^{+}CD45^{-}$、$CD34^{+}CD45^{-}CD11c^{+}$及$CD34^{+}CD45^{-}CD11b^{+}$群。

[0037] 定义

[0038] 术语“个体”、“宿主”、“受试者”和“患者”在本文中可互换使用,并且是指哺乳动物,包括但不限于人、非人灵长类动物(例如猿)、非人哺乳动物(例如,哺乳动物家畜动物(例如牛、猪、山羊和绵羊动物))和哺乳动物宠物(例如猫、狗);鱼;及鸟(例如鸡)。

[0039] “生物样品”包括从个体处获得的多种样品类型。该定义包括血液、血清、血浆及生物来源的其它液体样品;实体组织样品,如活检标本或来源于此的组织培养物或细胞及其子代。该定义还包括采集后以任何方式处置的样品,如用试剂处理;洗涤;或对某些细胞群如上皮细胞进行了富集。术语“生物样品”包括临床样品,并且还包括培养的细胞、细胞上清液、器官、组织样品、肺活检样品、肺上皮细胞、胃肠上皮细胞、胃肠道组织样品、支气管肺泡灌洗(BAL)液样品、鼻灌洗液样品、血液、血浆、血清、脑脊髓液、粪便样品等等。

[0040] “免疫调节剂(immunomodulator)”或“免疫调节剂(immunomodulatory agent)”为实现以下一项或多项的任何试剂:恢复阻抑的免疫功能、下调异常的免疫功能、调控异常/过度的免疫功能、增强正常免疫功能及提供所需免疫应答。免疫功能包括以下一种或多种:体液(抗体介导的)免疫、细胞免疫及先天免疫。“免疫调节剂”包括直接作用于免疫应答的

表达中所涉及的细胞或作用于细胞或分子机制的试剂，后一细胞或分子机制又用于改变免疫应答中所涉及的细胞的功能。免疫功能的调控可能是由于免疫调节剂消除由免疫系统内源性或外源性的正反馈影响所产生的活化机制的作用。免疫功能的调控可能是由于免疫调节剂消除由免疫系统内源性或外源性的负反馈影响所产生的抑制机制的作用。因此，免疫调节剂可具有不同的作用机制。

[0041] 术语“调节(modulate)”和“调节(modulation)”是指提高、降低或平衡免疫细胞、细胞因子、趋化因子、抗体、可溶性因子、表面分子、细胞内分子、效应子功能、调控功能等的数量和/或活性。

[0042] 术语“自身免疫疾病”和“自身免疫病症”在本文中可互换使用并且是指特征为对自体抗原的免疫应答、即对通常存在于体内的物质和组织的免疫应答的疾病。

[0043] 术语“炎性疾病”是指归因于、起因于或造成炎症的疾病。术语“炎性疾病”还可指的是由造成异常的组织损伤和/或细胞死亡的各种先天性和适应性免疫细胞引起放大应答的失调的炎症应答。

[0044] “佐剂”为能够增强免疫应答且因此为一类免疫强化剂的任何试剂(Stites和Terr,Basic and Clinical Immunology,第7版,Appleton and Lange Norwalk CT.第797页,1991)。佐剂在接种中用于增强免疫应答，以便增强体液和/或细胞介导的免疫应答。

[0045] “细胞因子”意指影响其它细胞的功能并且作为一种分子的任何分泌的多肽，该分子调节免疫或炎性应答中细胞之间的相互作用。细胞因子包括但不限于单核因子、趋化因子及淋巴因子，不管是哪些细胞产生了它们。

[0046] 术语“抗体”和“免疫球蛋白”包括任何同种型的抗体或免疫球蛋白、保留与抗原的特异性结合的抗体片段，包括但不限于Fab、Fv、scFv和Fd片段、嵌合抗体、人源化抗体、单链抗体、双特异性抗体、及包含抗体的抗原结合部分和非抗体蛋白质的融合蛋白。该术语还包括Fab’、Fv、F(ab’)$_2$和或保留与抗原的特异性结合的其它抗体片段、及单克隆抗体。抗体可为单价或二价的。

[0047] “治疗有效量”或“有效量”意指当为了治疗疾病而向哺乳动物或其它受试者施用时足以实现对于疾病的这种治疗的化合物或试剂的量。“治疗有效量”将根据化合物或试剂、疾病及其严重性以及有待治疗的受试者的年龄、重量、一般健康状况、性别等而变化。在一些情况下，试剂的“有效量”为以下量：1)恢复免疫功能至正常水平；2)调节免疫功能至正常水平；或3)降低免疫功能至低于病理水平。

[0048] 本文使用的术语“治疗(treatment)”、“治疗(treating)”等一般意指获得所需的药理和/或生理效果。该效果可以是完全或部分地抑制疾病或其症状的预防性效果，和/或可以是部分或完全的治愈疾病和/或可归因于该疾病的副作用的治疗性效果。如本文所用，“治疗”包括在哺乳动物中的疾病或症状的任何治疗，并且包括：(a)预防疾病或症状在可能易患该疾病或症状但尚未被诊断为患上该疾病的受试者中出现；(b)抑制疾病或症状，即阻止其发展；或(c)减轻疾病，即造成疾病的消退。治疗剂可在疾病或损伤发生之前、期间或之后施用。特别感兴趣的是治疗正发生的疾病，其中治疗使患者不希望的临床症状稳定或减轻。这种治疗理想地在受影响组织功能完全丧失之前进行。本疗法理想地在疾病的症状期期间施用，并且在一些情况下，在疾病的症状期之后施用。

[0049] “药学上可接受的载体或赋形剂”意指任何类型的无毒固体、半固体或液体填充

剂、稀释剂、包囊材料或配制助剂。制备制剂的本领域技术人员能够根据所选人的具体特征、需要治疗的疾病状态、疾病的阶段、和其它相关情况来容易地选择合适的给药形式和模式。

[0050] 在进一步描述本发明前，应理解本发明不限于所描述的具体实施方案，因为这些实施方案当然可以变化。还应该理解，本文所用的术语仅仅是为了描述具体的实施方案，并不意味着限制，因为本发明的范围只受所附权利要求书的限制。

[0051] 当提供一个数值范围时，应该理解的是介于该范围的上下限间的每一个中间值(除非文中另外清楚地指出，否则所述中间值是下限单位的十分之一)和任何其他所说明的或者在所说明的范围中的中间值都被包括在本发明内。这些较小范围的上下限可独立地被包括在该较小的范围中，且在所说明范围内明确地排除极限值的条件下也被包括在本发明内。当所述范围包括所述限值中的一个或两个时，排除了那些所包括的上下限中的一个或两个的范围也包括在本发明范围内。

[0052] 除非另外定义，否则本文所用的全部技术和科学术语都具有本发明相关领域的普通技术人员通常理解的相同含义。虽然类似于或等价于本文所述的那些的任何方法和材料还可用于实践或测试本发明，但现在描述示优选方法和材料。本文所提及的全部出版物以引用的方式并入本文，从而公开和描述了与出版物所引用的内容相关的方法和/或材料。

[0053] 除非文中另外清楚指出，否则必须指出如本文和所附权利要求书中所用，单数形式“一个(种)”和“所述”包括复数指示物。因此，例如，提及“活的新月柄杆菌”包括多个这种细菌且提及“细胞因子”包括提及本领域技术人员已知的一个或多个细胞因子及其等效物，诸如此类。还应该注意，权利要求书可能撰写成排除了任何可选要素。因此，此声明旨在用作排除性术语如“单独”、“仅仅”等与权利要求要素的陈述相关联的前提基础，或采用“负”限制。

[0054] 应当理解，为清楚起见在单独的实施方案的上下文中描述的本发明的某些特点也可在单个实施方案中以组合形式提供。相反，为简洁起见在参照单一实施方案的上下文中所描述的本发明的某些特点也可单独地或以任何适合的子组合方式给出。关于本发明的实施方案的所有组合具体地由本发明所涵盖并且在本文中公开就好象每个组合个别地和明确地公开一样。另外，各种实施方案及其要素的所有子组合也具体地由本发明所涵盖并且在本文中公开就好象每个这种子组合个别地且明确地在本文中公开一样。

[0055] 本文所讨论的出版物只提供在本申请的申请日之前的公开内容。本文中的任何内容都不能被解释为承认本发明无权使借助于在先发明的这种出版日期提前。此外，所提供的出版日期可能不同于实际的出版日期，实际的出版日期可能需要独立地确认。

[0056] 详述

[0057] 本公开涉及新月柄杆菌(CC)及其作为免疫调节性生物治疗剂的用途。已显示CC通过调节先天性和适应性免疫应答而具有免疫调节性作用。本公开提供包含活的新月柄杆菌(CC)的免疫调节组合物。本公开的免疫调节组合物可用于调节个体中的免疫应答。本公开的免疫调节组合物可用于减少个体中不希望的免疫应答。本公开的免疫调节组合物可用于减轻个体的炎症。本公开提供调节个体中的免疫应答的方法，所述方法涉及向所述个体施用包含CC的免疫调节组合物。本公开提供减少个体中不希望的免疫应答的方法，所述方法涉及向所述个体施用包含活CC的免疫调节组合物。本公开提供减轻个体的炎症的方法，所

述方法涉及向所述个体施用包含活CC的免疫调节组合物。

[0058] 免疫调节组合物

[0059] 本公开提供包含新月柄杆菌(CC)的免疫调节组合物。本公开的免疫调节组合物中的CC是活的。免疫调节组合物中的CC可为非变性的、突变的、减毒的和/或遗传修饰的。本公开的免疫调节组合物可包含新月柄杆菌的一种或多种不同菌株的混合物(cocktail)。

[0060] 含有CC的免疫调节组合物包含CC单独,且出于免疫调节活性而具有药学上可接受的载体或赋形剂,包括“佐剂”,其中CC向受试者的施用可完全不依赖于和/或在时间和/或在空间上与一种或多种抗原向受试者的施用分开,在受试者中需要调节或调控针对所述一种或多种抗原的免疫应答(例如,抗原特异性应答)。

[0061] 本公开的免疫调节组合物可调节(例如,降低个体中的免疫应答)。在一些情况下,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中的B细胞数量的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中的B细胞数量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中的B细胞数量至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%、至少100%(或2倍)、至少2.5倍、至少5倍、至少10倍或大于10倍的量。在一些情况下,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中的抗原特异性B细胞数量的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中的抗原特异性B细胞数量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中的抗原特异性B细胞数量至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%或大于75%的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中的自身抗原特异性B细胞数量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中的自身抗原特异性B细胞数量至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%或大于75%的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中的过敏原特异性B细胞数量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中的过敏原特异性B细胞数量至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%或大于75%的量。

[0062] 在一些情况下,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如降低)个体中的B细胞活性的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中的B细胞活化水平相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如降低)个体中的B细胞活化至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%、至少100%(或2倍)、至少2.5倍、至少5倍、至少10倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中的B细胞活化水平相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效降低个体中的B细胞活化至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%或大于75%的量。

[0063] 在一些情况下,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时

有效调节(例如减少)个体中对给定抗原有特异性的抗体的量的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中对给定抗原有特异性的抗体的量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中对所述抗原有特异性的抗体的量至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%、至少100%(或2倍)、至少2.5倍、至少5倍、至少10倍或大于10倍的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中对给定抗原有特异性的抗体的量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中对所述抗原有特异性的抗体的量至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%或大于75%的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中自身抗原特异性抗体的量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中自身抗原特异性抗体的量至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%或大于75%的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中过敏原特异性抗体的量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中过敏原特异性抗体的量至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%或大于75%的量。

[0064] 在一些情况下,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中一种或多种细胞因子产生的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中一种或多种细胞因子产生的量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中所述一种或多种细胞因子的产生至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%、至少100%(或2倍)、至少2.5倍、至少5倍、至少10倍或大于10倍的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中一种或多种细胞因子的产生相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中所述一种或多种细胞因子的产生至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%或大于75%的量。在其它情况下,与在不存在免疫调节组合物治疗下个体中GM-CSF的量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中GM-CSF的产生至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%、至少100%(或2倍)、至少2.5倍、至少5倍、至少10倍或大于10倍的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中GM-CSF的量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中GM-CSF的产生至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%或大于75%的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中IL-22的量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中IL-22的产生至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%、至少100%(或2倍)、至少2.5倍、至少5倍、至少10倍或大于10倍的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中IL-22

的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中IL-22的产生至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。在其它情况下，与在不存在免疫调节组合物治疗下个体中干扰素(IFN)-α或IFN-β或IFN-γ的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中IFN-α和/或IFN-β和/或IFN-γ的产生至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍或大于10倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中干扰素(IFN)-α和/或IFN-β和/或IFN-γ的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中干扰素(IFN)-α和/或IFN-β和/或IFN-γ的产生至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中IFN-γ的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中IFN-γ的产生至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0065] 作为另一个实例，在一些情况下，与在不存在免疫调节组合物治疗下个体中IL-1β、IL-17A、IL-2、IL-10、IL-6或TNF-α的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中IL-1β、IL-17A、IL-2、IL-10、IL-6或TNF-α的一种或多种的产生至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍或大于10倍的量。在一些情况下，与在不存在免疫调节组合物治疗下个体中IL-10的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效提高个体中IL-10的水平至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍或大于10倍的量。在一些情况下，与在不存在免疫调节组合物治疗下个体中产生IL-10的$CD4^+$和/或$CD8^+$T细胞的数量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效提高个体中产生IL-10的$CD4^+$和/或$CD8^+$T细胞的数量至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍或大于10倍的量。作为另一个实例，在一些情况下，与在不存在免疫调节组合物治疗下个体中IL-1β、IL-17A、IL-2、IL-6和TNF-α中的一种或多种的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中IL-1β、IL-17A、IL-2、IL-6和TNF-α中的一种或多种的产生至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中IL-17的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中IL-17的产生至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中IL-2的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中IL-2的产生至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少

40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中TNF-α的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中TNF-α的产生至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中IL-6的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中IL-6的产生至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中IL-1β的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中IL-1β的产生至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。在一些情况下，与在不存在免疫调节组合物治疗下个体中TGF-β的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效提高个体中TGF-β的水平至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍或大于10倍的量。

[0066] 在一些情况下，与在不存在免疫调节组合物治疗下个体中细胞因子、趋化因子或淋巴毒素如但不限于GM-CSF、IL-2、IL-22、干扰素、IL-1β、TGF-β、IL-17A、IL-2、IL-10、IL-6、IL-5、IL-13、TNF-α、IL-9、IL-28、KC/IL-8、MIP-1α、LTα4等的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如增加、减少或平衡)个体中一种或多种细胞因子、趋化因子或淋巴毒素如但不限于GM-CSF、IL-2、IL-22、干扰素、IL-1β、TGF-β、IL-17A、IL-2、IL-10、IL-6、IL-5、IL-13、TNF-α、IL-9、IL-28、KC/IL-8、MIP-1α、LTα4等的产生至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍或大于10倍的量。

[0067] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如降低)个体中的Th1应答的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中的Th1应答水平相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如降低)个体中的Th1应答至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中的Th1应答相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效降低个体中的Th1应答至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0068] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中$CD4^+$T细胞的数量和/或活性的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中$CD4^+$T细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中$CD4^+$T细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少

45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中抗原特异性$CD4^+$T细胞的数量和/或活性的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中抗原特异性$CD4^+$T细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中抗原特异性$CD4^+$T细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中$CD4^+$T细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中$CD4^+$T细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中抗原特异性$CD4^+$T细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中抗原特异性$CD4^+$T细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中自身抗原特异性$CD4^+$T细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中自身抗原特异性$CD4^+$T细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0069] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中$CD8^+$T细胞的数量和/或活性的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中$CD8^+$T细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中$CD8^+$T细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中抗原特异性$CD8^+$T细胞的数量和/或活性的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中抗原特异性$CD8^+$T细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中抗原特异性$CD8^+$T细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中$CD8^+$T的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中$CD8^+$T的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，与在不存在免疫调节组合

物治疗下个体中抗原特异性$CD8^+$T的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中抗原特异性$CD8^+$T的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中自身抗原特异性$CD8^+$T细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中自身抗原特异性$CD8^+$T细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0070] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中溶细胞性T细胞的数量和/或活性的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中溶细胞性T细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中溶细胞性T细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中抗原特异性溶细胞性T细胞的数量和/或活性的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中抗原特异性溶细胞性T细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中抗原特异性溶细胞性T细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中溶细胞性T细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中溶细胞性T细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中抗原特异性溶细胞性T细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中抗原特异性溶细胞性T细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0071] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节个体中自然杀伤(NK)细胞、NKT细胞、γδT细胞、先天性淋巴样细胞(ILC)、巨噬细胞和树突细胞(DC)中的一种或多种的数量和/或活性的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中NK细胞、NKT细胞、γδT细胞、ILC、巨噬细胞和DC中的一种或多种的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节个体中NK细胞、NKT细胞、γδT细胞、ILC、巨噬细胞和DC中的一种或多种的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10

倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中NK细胞、NKT细胞、γδT细胞、ILC、巨噬细胞和DC的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节个体中NK细胞、NKT细胞、γδT细胞、ILC、巨噬细胞和DC中的一种或多种的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0072] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节个体中调控性细胞的数量和/或活性的量。调控性T细胞(Treg)为$CD4^+$或$CD8^+$，并且还可为$FoxP3^+$。Treg还可由其它标记如PD-1、CTLA-4等定义。调控性细胞还可包含其它先天性细胞，如NK、NKT、γδT细胞、ILC和DC、及B淋巴细胞。NK和NKT也可为$FoxP3^+$并且也可由其它标记如PD-1定义。如本文所用，“调节调控性细胞的数量和/或活性”是指增加、减少或平衡调控性细胞的数量和/或活性。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中调控性细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节个体中调控性细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中调节性细胞的数量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效增加个体中调控性细胞的数量至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。作为一个实例，在一些情况下，与在不存在免疫调节组合物治疗下个体中$CD8^+$调控性细胞(例如，$CD8^+/CD25^+/FoxP3^+$细胞)的数量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效增加个体中$CD8^+$调控性细胞(例如，$CD8^+/CD25^+/FoxP3^+$细胞)的数量至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。作为另一个实例，在一些情况下，与在不存在免疫调节组合物治疗下个体中$CD8^+$控性性细胞(例如，$CD8^+/FoxP3^+$细胞)的数量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效增加个体中$CD8^+$调控性细胞(例如，$CD8^+/FoxP3^+$细胞)的数量至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。作为另一个实例，在一些情况下，与在不存在免疫调节组合物治疗下个体中NKT细胞(例如，$NKT^+/FoxP3^+$细胞)的数量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效增加个体中NKT细胞(例如，$NKT^+/FoxP3^+$细胞)的数量至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。作为另一个实例，在一些情况下，与在不存在免疫调节组合物治疗下个体中NKT细胞(例如，$NKT^+/PD\text{-}1^+$细

胞)的数量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效增加个体中NKT细胞(例如,$NKT^+/PD\text{-}1^+$细胞)的数量至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%、至少100%(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。作为另一个实例,在一些情况下,与在不存在免疫调节组合物治疗下个体中NK细胞(例如,$NK^+/FoxP3^+$细胞)的数量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效增加个体中NK细胞(例如,$NK^+/FoxP3^+$细胞)的数量至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%、至少100%(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。作为另一个实例,在一些情况下,与在不存在免疫调节组合物治疗下个体中NK细胞(例如,$NK^+/PD\text{-}1^+$细胞)的数量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效增加个体中NK细胞(例如,$NK^+/PD\text{-}1^+$细胞)的数量至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%、至少100%(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。作为另一个实例,在一些情况下,与在不存在免疫调节组合物治疗下个体中$CD4^+$调控性细胞(例如,$CD4^+/FoxP3^+$细胞)的数量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效增加个体中$CD4^+$调控性细胞(例如,$CD4^+/FoxP3^+$细胞)的数量至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%、至少100%(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。作为另一个实例,在一些情况下,与在不存在免疫调节组合物治疗下个体中$CD4^+$调控性细胞(例如,$CD4^+/CD25^+/FoxP3^+$细胞)的数量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效增加个体中$CD4^+$调控性细胞(例如,$CD4^+/CD25^+/FoxP3^+$细胞)的数量至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%、至少100%(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。

[0073] 在一些情况下,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中Th17细胞的数量和/或活性的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中Th17细胞的数量和/或活性相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中Th17细胞的数量和/或活性至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%、至少100%(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。在一些情况下,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中抗原特异性Th17细胞的数量和/或活性的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中抗原特异性Th17细胞的数量和/或活性相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中抗原特异性Th17细胞的数量和/或活性至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少

40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中Th17细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中Th17细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中抗原特异性Th17细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中抗原特异性Th17细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0074] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效标准化病理免疫应答的一种或多种血清标记的水平的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中CH、GLU、GLOB、ALT、AST、TP、PHOS、TRIG、URIC、CK、TBIL或尿素的水平相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效标准化一种或多种血清标记(这些标记包括但不限于胆固醇(CHOL)、葡萄糖(GLU)、球蛋白(GLOB)、丙氨酸转氨酶(ALT)、天冬氨酸转氨酶(AST)、总磷酸盐(TP)、总胆红素(TBIL)、磷酸盐(PHOS)、甘油三酯(TRIG)、尿酸(URIC)、肌酸激酶(CK)和尿素)的水平至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0075] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中Th22细胞的数量和/或活性的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中Th22细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中Th22细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中抗原特异性Th22细胞的数量和/或活性的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中抗原特异性Th22细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中抗原特异性Th22细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中Th22细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中Th22细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中抗原特异性Th22细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中抗原特异性Th22细胞的

数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0076] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节个体中TH9细胞的数量和/或活性的量。如本文所用，“调节TH9细胞的数量和/或活性”是指增加、减少或平衡TH9细胞的数量和/或活性。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中TH9细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节个体中TH9细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。

[0077] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如降低)和/或调控个体中的先天性和/或适应性(包括细胞和体液两种)免疫应答的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中一种或多种先天性或适应性免疫细胞和/或其效应子功能的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中先天性和/或适应性免疫细胞和/或其效应子功能的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中先天性和/或适应性免疫细胞和/或其效应子功能的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中先天性和/或适应性免疫细胞和/或其效应子功能的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0078] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效诱导和/或增加个体中先天性和/或适应性免疫细胞中的细胞凋亡以免发生不希望的炎症的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中一种或多种先天性或适应性免疫细胞的数量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效诱导和/或增加个体中先天性和/或适应性免疫细胞中的细胞凋亡至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。

[0079] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效诱导造血干细胞的增殖和/或分化并恢复体内平衡的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下的个体相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时在个体中有效诱导造血干细胞的增殖和/或分化并恢复体内平衡至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。

[0080] 在一些情况下，本公开的免疫调节组合物包含CC和抗原。当本公开的免疫调节组

合物包含CC和抗原时，在一些情况下，与在不存在免疫调节组合物治疗下针对抗原的免疫应答相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如降低)针对抗原的免疫应答至少约10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，当抗原为与自身抗原或过敏原相关或来源于自身抗原或过敏原的抗原时，与在不存在免疫调节组合物治疗下针对抗原的免疫应答相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如降低)针对抗原的免疫应答至少约10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，当免疫调节组合物包含单独或以组合形式的CC、抗原、自身抗原或过敏原时，在一些情况下，与在不存在免疫调节组合物治疗下个体中针对抗原的免疫应答相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效降低个体中针对抗原的免疫应答至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0081] 免疫应答可为体液免疫应答，例如B细胞或抗体免疫应答。因此，例如，在一些情况下，当抗原为与自身抗原或过敏原相关或来源于自身抗原或过敏原的抗原时，与在不存在免疫调节组合物治疗下针对抗原的B细胞应答相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如降低)针对抗原的B细胞应答至少约10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中针对抗原的B细胞应答相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效降低个体中针对抗原的B细胞应答至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，当抗原为与自身抗原或过敏原相关或来源于自身抗原或过敏原的抗原时，与在不存在免疫调节组合物治疗下对抗原有特异性的抗体的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)对抗原有特异性的抗体的量至少约10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中对抗原有特异性的抗体的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中对抗原有特异性的抗体的量至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0082] 免疫应答可为细胞免疫应答，例如T细胞应答。因此，例如，在一些情况下，当抗原为与自身抗原或过敏原相关或来源于自身抗原或过敏原的抗原时，与在不存在免疫调节组合物治疗下针对抗原的T细胞应答相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如降低)针对抗原的T细胞应答至少约10％、至少15％、至少

20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中针对抗原的T细胞应答相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效降低个体中针对抗原的T细胞应答至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。在一些情况下，免疫应答为体液免疫应答和细胞免疫应答。

[0083] 本公开的免疫调节组合物可包含每ml约10^3CC至每ml约10^{12}CC之量的CC。举例来说，本公开的免疫调节组合物可包含以下含量的CC：每ml约10^3CC至每ml约10^4CC、每ml约10^4CC至每ml约10^5CC、每ml约10^5CC至每ml约10^6CC、每ml约10^6CC至每ml约10^7CC、每ml约10^8CC至每ml约10^9CC、每ml约10^9CC至每ml约10^{10}CC、每ml约10^{10}CC至每ml约10^{11}CC、或每ml约10^{11}CC至每ml约10^{12}CC。

[0084] 本公开的免疫调节组合物可包含每mg约10^3CC至每mg约10^{12}CC之量的CC。举例来说，本公开的免疫调节组合物可包含以下含量的CC：每mg约10^3CC至每mg约10^4CC、每mg约10^4CC至每mg约10^5CC、每mg约10^5CC至每mg约10^6CC、每mg约10^6CC至每mg约10^7CC、每mg约10^8CC至每mg约10^9CC、每mg约10^9CC至每mg约10^{10}CC、每mg约10^{10}CC至每mg约10^{11}CC、或每mg约10^{11}CC至每mg约10^{12}CC。

[0085] 本公开的免疫调节组合物可包含每克约10^3CC至每克约10^{15}CC之量的CC。举例来说，本公开的免疫调节组合物可包含以下含量的CC：每克约10^3CC至每克约10^4CC、每克约10^4CC至每克约10^5CC、每克约10^5CC至每克约10^6CC、每克约10^6CC至每克约10^7CC、每克约10^8CC至每克约10^9CC、每克约10^9CC至每克约10^{10}CC、每克约10^{10}CC至每克约10^{11}CC、每克约10^{11}CC至每克约10^{12}CC、每克约10^{12}CC至每克约10^{13}CC、每克约10^{13}CC至每克约10^{14}CC、或每克约10^{14}CC至每克约10^{15}CC。

[0086] 本公开的免疫调节组合物可包含每单位剂型约10^2至约10^{20}个菌落形成单位(cfu)之量的CC；举例来说，本公开的免疫调节组合物可包含以下含量的CC：每单位剂型约10^2至约10^3、约10^3至约10^5、约10^5至约10^7、约10^7至约10^9、约10^9至约10^{11}、约10^{11}至约10^{13}、约10^{13}至约10^{15}、约10^{15}至约10^{18}、或约10^{18}至约10^{20}cfu。单位剂型可为以单剂量施用的量；例如，单位剂型可为0.5ml、1.0ml或适于以单剂量施用的其它体积。

[0087] CC可通过将新月柄杆菌暴露于约0℃至约37℃(例如，约0℃至15℃；约10℃至20℃；约20℃至25℃；约23℃至25℃；约23℃至37℃；或约30℃至35℃)的温度持续约1小时至延长的时间段(例如，至少1小时；至少2小时；至少4小时；过夜；至少24小时；至少48小时；至少100小时、或超过100小时)来制备。CC也可储存在盐水、磷酸盐缓冲盐水(PBS)或任何其它缓冲液中，在约36℃至-170℃(例如，约0℃至36℃；约0℃至4℃；约10℃至15℃；约0℃至-20℃；约-10℃及更低)的温度下，或在本领域技术人员已知的条件下。CC可为0.0000001至100％活的。例如，CC可为0.0000001至0.000001％活的、0.000001至0.00001％活的、0.00001至0.0001％活的、0.0001％至0.001％活的、0.001％至0.01％活的、0.01％至0.1％活的、0.1％至1％活的、1％至10％活的、10％至100％活的、25％至100活的、50％至100％活的、75％至100％活的、或90％至100％活的。

[0088] 本公开的免疫调节组合物可包含在培养基中以约0.10D至30.00D的各种光密度单

位(OD)生长的CC。例如,生长的CC培养物的OD可为0.1、0.2、0.3、0.4、0.5、0.6、0.7、0.8、0.9等。

[0089] 新月柄杆菌

[0090] 本公开的免疫调节组合物包含柄杆菌属,其中柄杆菌属为非病原的。非病原柄杆菌属包括19种不同种,包括不粘柄菌属(Asticcacaulis)的两个种(弧形柄杆菌、黑柄杆菌(C.henricii)、中间柄杆菌、锈棕色柄杆菌(C.robiginosus)、金红柄杆菌(C.rutilis)、副弧形柄杆菌(C.subvibriodes)、梭状柄杆菌、罗西柄杆菌(C.rossii)、离中不粘柄菌、双鞘不粘柄菌等)。参见,例如JS Poindexter,The Caulobacters:Ubiquitous Unusual Bacteria,Microbiol Rev 45,123-179,1981)。若干柄杆菌属可从美国典型培养物保藏中心(ATCC)获得,如CB35、CB26、CB28、KA5、CB66、FC4等。呈活的、非变性、突变或减毒形式的柄杆菌属的所有这些物种都可用作本文所述的免疫调节剂。另外,柄杆菌属细菌可呈不活动的柄、能动的游动细胞、粗短的鞭毛蛋白和鞭毛蛋白阳性的、鞭毛蛋白阴性的、分裂和/或非分裂的形式。柄杆菌属可在以下条件下生长:18℃-42℃范围内的温度,和5-9范围内的pH,但最佳在23-25℃范围内的温度和pH 7下于PYE培养基中。突变或遗传修饰形式的柄杆菌属可通过以下方式产生:改变培养条件的营养素、化学品、pH、温度、紫外线或红外线、辐射等;或遗传修饰活细菌中的各种酶、代谢途径、表面分子、核酸、质粒、细胞和细胞壁组分、光滑和粗糙的LPS(JS Poindexter,The Caulobacters:Ubiquitous Unusual Bacteria,Microbiol Rev 45,123-179,1981)。

[0091] 新月柄杆菌可充当递送抗原的载体和/或递送媒介物。作为非遗传修饰(GM),如静电和疏水相互作用,抗原与新月柄杆菌表面的结合可使新月柄杆菌能够充当抗原载体和/或递送媒介物。此外,由于生物粘附/粘膜粘附,所以新月柄杆菌可通过M细胞转运、递送至DC/APC及DC/APC的后续调节、在粘膜表面处的NK、NKT、B和T细胞应答的调节来促进抗原摄取。

[0092] 虽然以下论述集中于新月柄杆菌,但多种非病原柄杆菌属物种中的任一种均可包含在本公开的免疫调节组合物中。

[0093] 在一些情况下,本公开的免疫调节组合物包含新月柄杆菌(CC)。在一些情况下,新月柄杆菌为野生型。在一些情况下,新月柄杆菌为脂多糖阴性菌株。在一些情况下,新月柄杆菌为S层阴性菌株。在一些情况下,CC为突变、减毒的,或含有自杀突变。在一些情况下,新月柄杆菌有或没有耐药性质粒,如氯霉素、青霉素耐药性质粒。在一些情况下,新月柄杆菌可生长在除PYE培养基外的其它培养基中。

[0094] 在一些情况下,新月柄杆菌被遗传修饰以产生一种或多种异源多肽。所述多肽可具有广泛多种尺寸。合适的异源多肽包括但不限于PD1、PDL、CTLA-4、GITR、VISTA;抗原呈递细胞(APC)或T细胞上所见的共抑制性蛋白;细胞因子(例如,IL-10;或以上列出的细胞因子中的任一种);趋化因子;抗原(例如,如上文所述的自身抗原或过敏原);针对以下的抗体:抗原(例如,自身抗原;如上文所述)、信号传导分子、受体、细胞因子、促细胞凋亡蛋白;融合蛋白(例如,抗原与细胞因子、抗原与载体蛋白)等。

[0095] 在一些情况下,新月柄杆菌通过用荧光、放射性同位素、光标签等标记或偶联细菌来修饰。

[0096] 在一些情况下,新月柄杆菌为遗传修饰的。在一些情况下,新月柄杆菌被遗传修饰

以使得微生物是减毒的。在一些情况下，新月柄杆菌的核酸被修饰以使得微生物对于增殖是减毒的。

[0097] 在一些情况下，本公开的免疫调节组合物包含整个CC。在一些情况下，本公开的免疫调节组合物包含活的或非变性的CC。在一些情况下，本公开的免疫调节组合物包含CC的个别或多个组分、副产物和/或代谢物，其可在其它合成或天然细菌细胞中分离、合成或基因制造作为合成生物素。CC的组分可包括但不限于效应分子，例如多糖、糖基神经酰胺、肽聚糖、核酸、结构蛋白、短链脂肪酸、脂肪酸代谢物、羟基脂肪酸等。新月柄杆菌的级分、组分、副产物和/或代谢物可通过以下操作获得：过滤培养上清液，用各种有机溶剂、酶如糖苷酶、脂肪酶、DNA酶、RNA酶、蛋白酶、溶菌酶等处理。在一些情况下，本公开的免疫调节组合物包含CC的个别或多个组分，可使用物理化学或遗传方法将其与抗原融合并用作合成细菌。

[0098] 在一些情况下，新月柄杆菌在其外膜囊泡中被生物工程化以包装和递送化疗剂和/或免疫治疗剂及来自其它细菌的合成遗传物质。在一些情况下，新月柄杆菌被生物工程化并构建到基因回路中作为合成治疗细菌，“合成生物素”。

[0099] 在一些情况下，本公开的免疫调节组合物包含CC的S层。在一些情况下，本公开的免疫调节组合物包含CC的S层，其经遗传修饰以展示一种或多种异源多肽、化疗剂和/或免疫治疗剂。在一些情况下，本公开的免疫调节组合物包含S层的组分。

[0100] 抗原

[0101] 本公开的免疫调节组合物除CC之外还可包含一种或多种(例如1、2、3、4、5、6、7、8、9、10或超过10种)抗原。合适的抗原包括但不限于来源于自身抗原和过敏原的抗原。

[0102] 在一些实施方案中，新月柄杆菌经遗传修饰以产生抗原；并且经遗传修饰的新月柄杆菌为活的，以产生本公开的免疫调节组合物。遗传修饰细菌的方法是本领域中已知的。

[0103] 在其它实施方案中，CC在本公开的免疫调节组合物中与抗原混合。新月柄杆菌可充当递送抗原的载体和/或递送媒介物。作为非遗传修饰(GM)，如静电和疏水相互作用，抗原与新月柄杆菌表面的结合可使新月柄杆菌能够充当抗原载体和/或递送媒介物。此外，由于生物粘附/粘膜粘附，所以新月柄杆菌可通过M细胞转运、递送至DC/APC及DC/APC的后续调节、在粘膜表面处的NK、NKT、B和T细胞应答的调节来促进抗原摄取。

[0104] 用于本文所述的免疫调节组合物及采用CC的方法的某些实施方案中的抗原可为任何指表位、分子、分子复合物、细胞或组织，在受试者中需要调节针对它们的免疫原性。

[0105] 本公开的免疫调节组合物可包含一种或多种抗原或抗原性组合物，其能够调节针对人或动物自身抗原或过敏原的免疫应答。抗原可与自身免疫疾病、过敏、哮喘、朊病毒疾病或其中抗原特异性应答的调节将为需要或有益的任何其它病状有关。

[0106] 合适的抗原可为本领域中已知的任何类型的抗原。抗原可由以下多种来源中的任一种产生：如植物、动物、原核生物、体外细胞培养物等。抗原可呈如下所述的多种形式。

[0107] 合适的抗原包括例如肽、修饰的肽、肽拟表位、构形上受限的合成肽、来自一种或多种抗原的多表位肽、分支肽、脂肽、单脂肽、二脂肽、与蛋白质缀合或融合的肽、与T细胞或B细胞表位缀合或融合的肽。参见，例如美国专利号8,198,400。合适的抗原包括例如全长抗原、截短抗原、突变抗原、及灭活或组合形式。合适的抗原包括例如蛋白质、纯化或重组蛋白、重组融合蛋白、与toll样受体(TLR)激动剂/拮抗剂缀合的蛋白质和肽、与细菌毒素缀合的蛋白质和肽、与抗体缀合的蛋白质和肽、与细胞因子和趋化因子缀合的蛋白质和肽、糖蛋

白、糖脂蛋白及其衍生物。合适的抗原包括例如多糖、多糖缀合物、寡糖、脂质、糖脂、碳水化合物及其衍生物。抗原可被修饰以调节抗原呈递和/或共抑制、或增强共抑制信号。

[0108] 抗原或抗原性组合物可由自身抗原、过敏原等获得。

[0109] 抗原可为全细胞提取物、细胞溶胞产物、全细胞、全活细胞、全灭活细胞、全辐射细胞等。抗原可为粗的、纯化的或重组的形式。在一些情况下，抗原为至少50％纯的、至少60％纯的、至少70％纯的、至少80％纯的、至少90％纯的、至少95％纯的、至少98％纯的、或至少99％纯的、或大于99％纯的。

[0110] 抗原可以化学方式、酶方式或遗传方式偶联到CC上。在一些情况下，抗原以与CC混合的形式存在于本公开的免疫调节组合物中。

[0111] 本公开的免疫调节组合物可包含单一类型的抗原。本公开的免疫调节组合物可包含2种或更多种不同的抗原。本公开的免疫调节组合物可包含2、3、4、5、6或大于6种不同的抗原。当本公开的免疫调节组合物包含一种以上抗原时，所述一种以上抗原可来自相同的细胞或过敏原。当本公开的免疫调节组合物包含一种以上抗原时，所述一种以上抗原可来自两种或更多种细胞或过敏原。

[0112] 抗原可呈蛋白质、脂多糖、脂蛋白、蛋白多糖、糖蛋白、粘多糖、寡糖等形式。

[0113] 抗原可呈包含编码抗原(例如多肽抗原)的核苷酸序列的核酸形式。例如，抗原可以DNA(例如，质粒DNA、裸DNA等)、RNA和/或野生型、减毒的和/或基于重组载体的核酸形式提供。编码抗原的核酸可为“裸的”或包含于如脂质体的递送系统中。

[0114] 编码抗原的重组载体可为至少一种重组表达构建体，其包含与在以下各物中编码抗原的核苷酸序列可操作地连接的启动子：重组病毒载体(如腺病毒(例如Ad2、Ad4、Ad5、Ad35、Ad35K5等)、腺相关病毒、慢病毒、疱疹病毒、痘病毒、水疱性口腔炎病毒、α病毒、麻疹病毒、番木瓜花叶病毒、巨细胞病毒、修饰的牛痘安卡拉病毒MVA、脊髓灰质炎病毒、Marba病毒等)、细菌载体疫苗(如沙门氏菌属(Salmonella)、志贺氏菌属(Shigella)、大肠埃希氏菌(E.coli)、乳酸乳球菌(Lactococcus lactis)、李斯特氏菌属某种(Listeria sp.)、乳杆菌属某种(Lactobacillus sp.))、真菌载体(如热杀的重组酵母属(Saccharomyces)酵母)、植物病毒、病毒样颗粒(VLP)、病毒体、合成疫苗颗粒、合成仿生超分子生物载体、去病原化病毒/菌株(如来自H5N1的NIBRG14)。载体可呈活的野生型、非复制型、突变的、修饰的、有缺陷的或减毒的形式。载体可来自人、动物、植物或原核生物来源并且以任何有效量。

[0115] 在治疗或预防自身免疫疾病或过敏时，抗原可在与本公开的免疫调节组合物相同或不同的时间、相同或不同的位点给予。

[0116] 自身抗原

[0117] 在一些情况下，除CC之外，本公开的免疫调节组合物还包含自身抗原。在一些情况下，除CC之外，本公开的免疫调节组合物还包含来自一种或多种自身组织的一种或多种自身抗原，例如1、2、3、4、5或更多种抗原。

[0118] 例如，当自身免疫疾病为1型糖尿病时，抗原可为胰岛β细胞相关抗原、胰岛素原、谷氨酸脱羧酶、嗜铬粒蛋白A、胰岛淀粉状多肽HSP60；为全身性红斑狼疮时，抗原可为snRNP；为格雷夫氏病(Grave’s disease)时，抗原可为甲状腺球蛋白、促甲状腺激素受体或甲状腺上皮细胞；为血小板减少性紫癜时，抗原可为血小板、GPIIB/IIIa；为多发性硬化症时，抗原可为髓鞘碱性蛋白、MOG、PLP；为乳糜泻时，抗原可为转谷氨酰胺酶。

[0119] 合适的自身抗原可为牵涉于自身免疫疾病的发生和/或传播中的自身抗原，其病理可归因于对由相关靶器官、组织或细胞表达的分子有特异性的抗体的存在，例如全身性红斑狼疮(SLE)或重症肌无力(MG)。在这种疾病中，可能期望将针对相关自身抗原的进行中的抗体介导(即Th2型)的免疫应答导向细胞(即Th1型)免疫应答。或者，可期望通过预防性地诱导针对适当自身抗原的Th1应答来预防未患有但疑似易患相关自身免疫疾病的受试者中针对自身抗原的Th2应答的发作或降低该应答的水平。可包括在本发明的免疫调节组合物中的自身抗原包括但不限于：(a)对于SLE，是史密斯蛋白(Smith protein)、RNP核糖核蛋白、及SS-A和SS-B蛋白；和(b)对于MG，是乙酰胆碱受体。牵涉于一种或多种类型的自身免疫应答中的其它抗原的实例包括例如内源性激素，如黄体生成素、卵泡刺激素、睾丸素、生长激素、催乳素及其它激素。

[0120] 合适的自身抗原的其它实例包括与以下疾病有关的抗原：神经疾病，如精神分裂症、阿尔茨海默氏病(Alzheimer's disease)、抑郁症、垂体机能减退；及心血管疾病，如动脉粥样硬化(例如，对于动脉粥样硬化的抗原可为胆固醇酯转移蛋白、氧化型LDL、apoB210、apoB100)等。

[0121] 本领域技术人员将认识到其它合适的自身抗原包括与幼年型类风湿性关节炎和马施二氏强直性脊柱炎(Marie-Strumpell ankylosing spondylitis)有关的那些抗原，其可能造成前葡萄膜炎及继发的青光眼。其它合适的自身抗原包括与亨廷顿氏病(Huntington's disease)和帕金森氏病(Parkinson's disease)有关的那些抗原。

[0122] 自身抗原的实例包括与细胞或器官特异性自身免疫有关的那些。这种自身抗原包括乙酰胆碱受体，与重症肌无力有关；肌动蛋白，与慢性活动性肝炎和原发性胆汁性肝硬化有关；腺嘌呤核苷酸易位体(ANT)，与扩张型心肌病和心肌炎有关；β-肾上腺素受体，与扩张型心肌病有关；芳族L-氨基酸脱羧酶，与I型自身免疫性多内分泌腺病综合征(APS-I)有关；脱唾液酸糖蛋白受体，与自身免疫性肝炎有关；杀细菌/渗透性增强蛋白(Bpi)，与囊性纤维化脉管炎有关；钙敏感受体，与获得性甲状旁腺功能减退有关；胆固醇侧链断裂酶(CYPIIa)，与APS-I有关；胶原IV型α_3-链，与古德帕斯彻综合征(Goodpasture syndrome)有关；细胞色素P450 2D6(CYP2D6)，与自身免疫性肝炎有关；肌间线蛋白，与克罗恩氏病(Crohn disease)和冠状动脉病有关；桥粒芯蛋白1，与落叶状天疱疮有关；桥粒芯蛋白3，与寻常天疱疮有关；F-肌动蛋白，与自身免疫性肝炎有关；GM神经节苷脂，与格林巴利综合征(Guillain-Barrésyndrome)有关；谷氨酸脱羧酶(GAD65)，与1型糖尿病和僵人综合征有关；谷氨酸受体(GLUR)，与拉斯马森脑炎(Rasmussen encephalitis)有关；H/K ATP酶，与自身免疫性胃炎有关；17-α-羟化酶(CYP17)，与APS-I有关；21-hydroxylast(CYP21)，与艾迪生病(Addison disease)有关；IA-2(ICA512)，与1型糖尿病有关；胰岛素，与1型糖尿病和胰岛素低血糖综合征(平田病(Hirata disease))有关；胰岛素受体，与B型胰岛素抗性、棘皮症和全身性红斑狼疮(SLE)有关；1型内因子，与恶性贫血有关；白细胞功能相关抗原(LFA-1)，与治疗抗性莱姆关节炎(Lyme arthritis)有关；髓磷脂相关糖蛋白(MAG)，与多发性神经病有关；髓鞘碱性蛋白，与多发性硬化症和脱髓鞘疾病有关；髓磷脂少突胶质细胞糖蛋白(MOG)，与多发性硬化症有关；减数分裂(myosis)，与风湿热有关；p-80-coilin，与特应性皮炎有关；丙酮酸脱氢酶复合体-E2(PDC-E2)，与原发性胆汁性肝硬化有关；碘化钠同向转运体(NIS)，与巴塞多化甲状腺肿和自身免疫性甲状腺机能减退有关；SOX-10，与白斑病有关；

甲状腺和眼肌共享蛋白，与甲状腺相关眼病有关；甲状腺球蛋白，与自身免疫性甲状腺炎有关；甲状腺过氧化物酶，与自身免疫性桥本氏甲状腺炎(Hashimoto thyroiditis)有关；促甲状腺素受体，与格雷夫氏病有关；组织转谷氨酰胺酶，与腹腔病有关；转录辅激活物p75，与特应性皮炎有关；色氨酸羟化酶，与APS-I有关；酪氨酸酶，与白斑病和转移性黑色素瘤有关；以及酪氨酸羟化酶，与APS-I有关。

[0123] 自身抗原的实例包括与系统自身免疫有关的那些。这种自身抗原包括ACTH，与ACTH缺乏症有关；氨酰tRNA组氨酰合成酶，与肌炎和皮肌炎有关；氨酸tRNA合成酶(几种)，与多发性肌炎和皮肌炎有关；心磷脂，与SLE有关；碳酸酐酶II，与SLE、斯耶格伦综合征(Sjögren syndrome)和全身性硬化有关；胶原(多种类型)，与类风湿性关节炎(RA)、SLE和进行性全身性硬化有关；着丝点相关蛋白，与全身性硬化有关；DNA依赖性核小体刺激ATP酶，与皮肌炎有关；纤维蛋白，与硬皮病有关；纤连蛋白，与SLE、RA和硬斑病有关；葡萄糖-6-磷酸异构酶、与RA有关；β2-糖蛋白I(β2-GPI)，与原发性抗磷脂综合征有关；高尔基体蛋白(95、97、160、180)，与斯耶格伦综合征、SLE和RA有关；热休克蛋白，与各种免疫相关病症有关；半桥粒蛋白180，与大疱性类天疱疮、妊娠疱疹和瘢痕性类天疱疮有关；组蛋白H2A-H2B-DNA，与SLE有关；IgE受体，与慢性特发性荨麻疹有关；角蛋白，与RA有关；Ku-DNA-蛋白激酶，与SLE有关；Ku-核蛋白，与结缔组织综合征有关；La磷蛋白(La 55-B)，与斯耶格伦综合征有关；髓过氧化物酶，与坏死性和新月体性肾小球性肾炎及系统性血管炎有关；蛋白酶3(PR3)，与韦格纳肉芽肿病(Wegener granulomatosis)和丘-施二氏综合征(Churg-Strauss syndrome)有关；RNA聚合酶I-III(RNP)，与全身性硬化和SLE有关；信号识别蛋白(SRP54)，与多发性肌炎有关；拓扑异构酶-I(Scl-70)，与硬皮病和雷诺综合征(Raynaud syndrome)有关；微管蛋白，与慢性肝病和内脏利什曼虫病(visceral leishmaniasis)有关；以及波形蛋白，与系统性自身免疫病有关。

[0124] 自身抗原的其它实例包括与血浆蛋白和细胞因子自身免疫有关的那些。这种自身抗原包括C1抑制剂，与自身免疫性C1缺乏症有关；C1q，与SLE和膜增生性肾小球性肾炎(MPGN)有关；细胞因子(IL-1α、IL-1β、IL-6、IL-10、LIF)，与RA和全身性硬化有关；因子II、因子V、因子VII、因子VIII、因子IX、因子X、因子XI、因子XII、凝血酶、vWF，与延长的凝血时间有关；糖蛋白IIb/IIIg和1B/IX，与自身免疫性血小板减少性紫癜有关；IgA，与免疫缺陷有关；以及氧化的LDL(OxLDL)，与动脉粥样硬化有关。

[0125] 自身抗原的又一些实例包括与癌症和副肿瘤自身免疫有关的那些。这种自身抗原包括双载蛋白，与神经元病和小肺细胞癌有关；周期素B1，与肝细胞癌有关；DNA拓扑异构酶II，与肝癌有关；桥粒斑蛋白，与副肿瘤天疱疮有关；桥尾蛋白，与副肿瘤僵人综合征有关；Hu蛋白，与副肿瘤脑脊髓炎有关；神经元烟碱乙酰胆碱受体，与亚急性自主神经病变有关；p53，与癌症和SLE有关；p62(IGF-II mRNA结合蛋白)，与肝细胞癌(China)有关；恢复蛋白，与癌症相关视网膜病有关；Ri蛋白，与副肿瘤眼阵挛肌阵挛共济失调有关；βIV膜收缩蛋白，与下运动神经元综合征有关；突触结合蛋白，与兰伯特-伊顿肌无力综合征(Lambert-Eaton myasthenic syndrome)有关；电压门控钙通道，与与兰伯特-伊顿肌无力综合征有关；以及Yo蛋白，与副肿瘤小脑变性有关。

[0126] 过敏原

[0127] 在一些情况下，除CC之外，本公开的免疫调节组合物还包含过敏原。合适的过敏原

可使用已知方法获得和/或产生。合适的过敏原的类别包括但不限于花粉、除猫毛屑以外的动物毛屑、草、霉菌、粉尘、抗生素、带刺昆虫的毒液、以及多种环境(包括化学品和金属)、药物和食品过敏原。常见的树过敏原包括来自以下的花粉:三角叶杨、杨树、岑树、桦树、枫树、橡树、榆树、山核桃树及美洲山核桃树;常见植物过敏原包括来自艾蒿、豚草、英国车前草、酸模(sorrel-dock)及藜的那些;植物接触过敏原包括来自毒栎、毒葛及荨麻的那些;常见的草过敏原包括黑麦草、提摩西草(Timothy)、蒋森草(Johnson)、百慕大草(Bermuda)、牛毛草及蓝草过敏原;常见的过敏原还可从霉菌或真菌中获得,如链格孢属(Alternaria)、镰刀菌属(Fusarium)、单孢枝霉菌属(Hormodendrum)、曲菌属(Aspergillus)、小多孢菌属(Micropolyspora)、毛霉属(Mucor)及嗜热放线菌(thermophilic actinomycetes);表皮过敏原可从房屋或有机粉尘(通常是真菌来源)、节肢动物如嗜甜家螨(屋尘螨(Dermatophagoides pteronyssinus))或动物来源如羽毛和狗毛屑处获得;常见的食品过敏原包括奶和奶酪(diary)、蛋、小麦、坚果(例如花生)、海鲜(例如贝类)、豌豆、豆及面筋过敏原;常见的环境过敏原包括金属(镍和金)、化学品(甲醛、三硝基苯酚及松节油)、胶乳、橡胶、纤维(棉花或羊毛)、粗麻布、染发剂、化妆品、清洁剂及芳香剂过敏原;常见的药物过敏原包括局部麻醉剂和水杨酸盐过敏原;抗生素过敏原包括青霉素、四环素及磺酰胺过敏原;且常见的昆虫过敏原包括蜜蜂、黄蜂和蚁毒液、及蟑螂萼过敏原。尤其充分表征的过敏原包括但不限于Der p I过敏原的主要和隐蔽表位(Hoyne等人(1994)Immunology 83190-195),bee venom phospholipase A2(PLA)(Akdis等人(1996)J.Clin.Invest.98:1676-1683),birch pollen allergen Bet v 1(Bauer等人(1997)Clin.Exp.Immunol.107:536-541)以及the multi-epitopic recombinant grass allergen rKBG8.3(Cao等人(1997)Immunology 90:46-51)。这些及其它合适的过敏原可商购获得和/或可按照已知技术作为提取物容易地制备。

[0128] 合适的过敏原包括树木花粉过敏原、杂草花粉过敏原、药草花粉过敏原、青草花粉过敏原、螨过敏原、昆虫过敏原、毒液过敏原、动物毛发过敏原、毛屑过敏原及食品过敏原。

[0129] 在一些情况下,过敏原呈提取物、纯化的过敏原、修饰的过敏原或重组过敏原或重组过敏原的突变体或其任何组合的形式。在一些情况下,过敏原选自由以下组成的组:青草花粉过敏原、尘螨过敏原、豚草过敏原、猫过敏原及桦树过敏原。

[0130] 过敏原可以每单位剂型约2.5μg至约75μg的量存在于本公开的免疫调节组合物中。例如,过敏原可以每单位剂型以下的量存在于本公开的免疫调节组合物中:约2.5μg至约5μg、约5μg至约10μg、约10μg至约15μg、约15μg至约20μg、约20μg至约25μg、约25μg至约50μg、或约50μg至约75μg、或大于75μg。

[0131] 在一些情况下,包含过敏原的本公开的免疫调节组合物的剂量具有约65至约17,600个生物过敏原单位(BAU)的效力。在一些情况下,包含过敏原的本公开的免疫调节组合物的剂量包括约650BAU至约6,000BAU。

[0132] 抗体

[0133] 在一些情况下,除CC之外,本公开的免疫调节组合物还包含针对癌抗原、自身抗原、过敏原或致病抗原的抗体(例如,治疗性抗体、单克隆抗体、双特异性抗体、化学免疫缀合抗体、放射免疫缀合抗体、抗体-细胞因子融合蛋白、抗体-抗原融合蛋白、抗体-免疫毒素融合蛋白等)。

[0134] 可包括在本公开的免疫调节组合物中的抗体包括但不限于针对共刺激或共抑制分子(CD28、CD40、CTLA-4、PD-1、PDL-1、GITR、VISTA、LAG-3、ICOS、CD137、OX40、CD137、CD227、CTLA-4、KIR、TCR、TIM3等)的抗体;及其它治疗性抗体。

[0135] 合适抗体的非限制性实例包括但不限于阿达木单抗、贝伐单抗、英夫利昔单抗、阿昔单抗、阿来组单抗、巴匹珠单抗、巴利昔单抗、贝利单抗、巴列津单抗、布罗达单抗、康纳单抗、塞妥珠单抗、西妥昔单抗、西他土珠(conatumumab)、地诺单抗、依库珠单抗、etrolizumab、吉妥单抗奥佐米星、格里木单抗、替伊莫单抗、拉贝珠单抗、马帕妥木单抗、马妥珠单抗、美泊利单抗、莫维珠单抗、莫罗单抗-CD3、那他珠单抗、尼妥珠单抗、奥法木单抗、奥马佐单抗、奥戈伏单抗、帕利珠单抗、帕尼单抗、pemtumornab、帕妥珠单抗、兰尼单抗、利妥昔单抗、罗维珠单抗、托珠单抗、托西莫单抗、曲妥单抗、优特克单抗、维多珠单抗、扎鲁木单抗及扎木单抗。

[0136] 可与本公开的免疫调节组合物组合使用的治疗性和预防性抗体的非限制性实例包括MDX-010(Medarex,N.J.),其为用于治疗前列腺癌的人源化抗CTLA-4抗体;SYNAGIS™(MedImmune,Md.),其为用于治疗RSV感染的人源化抗呼吸道合胞病毒(RSV)单克隆抗体;及HERCEPTIN™(曲妥单抗)(Genentech,Calif.),其为用于治疗转移性乳腺癌的人源化抗HER2单克隆抗体。其它实例为人源化抗CD18F(ab')$_2$(Genentech);CDP860,其为人源化抗CD18F(ab')$_2$(Celltech,UK);PRO542,其为与CD4融合的抗HIV gp120抗体(Progenics/Genzyme Transgenics);奥司他韦,其为人抗乙型肝炎病毒抗体(Protein Design Lab/Novartis);PROTOVIR™,其为人源化抗CMV IgGI抗体(Protein Design Lab/Novartis);MAK-195(SEGARD),其为鼠抗TNF-αF(ab')$_2$(Knoll Pharma/BASF);IC14,其为抗CD14抗体(ICOS Pharm);人源化抗VEGF IgG1抗体(Genentech);OVAREX™,其为鼠抗CA 125抗体(Altarex);PANOREX™,其为鼠抗17-IA细胞表面抗原IgG2a抗体(Glaxo Wellcome/Centocor);BEC2,其为鼠抗独特型(GD3表位)IgG抗体(ImClone System);IMC-C225,其为嵌合抗EGFR IgG抗体(ImClone System);VITAXIN™,其为人源化抗αVβ3整联蛋白抗体(Applied Molecular Evolution/MedImmune);Campath 1H/LDP-03,其为人源化抗CD52IgG1抗体(Leukosite);Smart M195,其为人源化抗CD33IgG抗体(Protein Design Lab/Kanebo);RITUXAN™,其为嵌合抗CD20IgG1抗体(IDEC Pharm/Genentech,Roche/Zettyaku);LYMPHOCIDE™,其为人源化抗CD22IgG抗体(Immunomedics);Smart ID10,其为人源化抗HLA抗体(Protein Design Lab);ONCOLYM™(Lym-1),其为放射性同位素标记的鼠抗HLA诊断试剂(DIAGNOSTIC REAGENT)抗体(Techniclone);ABX-IL8,其为人抗IL8抗体(Abgenix);抗CD11a,其为人源化IgG1抗体(Genentech/Xoma);ICM3,其为人源化抗ICAM3抗体(ICOS Pharm);IDEC-114,其为灵长类动物源化抗CD80抗体(IDEC Pharm/Mitsubishi);ZEVALIN™,其为放射性同位素标记的鼠抗CD20抗体(IDEC/Schering AG);IDEC-131,其为人源化抗CD40L抗体(IDEC/Eisai);IDEC-151,其为灵长类动物源化抗CD4抗体(IDEC);IDEC-152,其为灵长类动物源化抗CD23抗体(IDEC/Seikagaku);SMART抗CD3,其为人源化抗CD3IgG(Protein Design Lab);5G1.1,其为人源化抗补体因子5(C5)抗体(Alexion Pharm);D2E7,其为人源化抗TNF-α抗体(CAT/BASF);CDP870,其为人源化抗TNF-αFab片段(Celltech);IDEC-151,其为灵长类动物源化抗CD4IgG1抗体(IDEC Pharm/SmithKline Beecham);MDX-CD4,其为人抗CD4IgG抗体(Medarex/Eisai/Genmab);CDP571,其为人源化抗TNF-αIgG4抗体(Celltech);LDP-02,其为

人源化抗α4β7抗体(LeukoSite/Genentech);OrthoClone OKT4A,其为人源化抗CD4IgG抗体(Ortho Biotech);ANTOVA™,其为人源化抗CD40L IgG抗体(Biogen);ANTEGREN™,其为人源化抗VLA-4IgG抗体(Elan);MDX-33,其为人抗CD64(FcγR)抗体(Medarex/Centeon);SCH55700,其为人源化抗IL-5IgG4抗体(Celltech/Schering);SB-240563和SB-240683,其分别为人源化抗IL-5和IL-4抗体(SmithKline Beecham);rhuMab-E25,其为人源化抗IgE IgG1抗体(Genentech/Norvartis/Tanox Biosystems);ABX-CBL,其为鼠抗CD-147IgM抗体(Abgenix);BTI-322,其为大鼠抗CD2IgG抗体(MedImmune/Bio Transplant);Orthoclone/OKT3,其为鼠抗CD3IgG2a抗体(ortho Biotech);SIMULECT™,其为嵌合抗CD25IgG1抗体(Novartis Pharm);LDP-01,其为人源化抗β_2-整联蛋白IgG抗体(LeukoSite);抗LFA-1,其为鼠抗CD18F(ab')$_2$(Pasteur-Merieux/Immunotech);CAT-152,其为人抗TGF-β_2抗体(Cambridge Ab Tech);以及Corsevin M,其为嵌合抗因子VII抗体(Centocor)。以上列出的免疫反应剂以及任何其它免疫反应剂可根据本领域技术人员已知的任何方案来施用,包括由免疫反应剂的供应商所推荐的方案。

[0137] 可与本公开的免疫调节组合物组合使用的治疗性和预防性抗体的其它实例包括阿达木单抗和英利昔单抗(Remicade);ACTEMRA™(Genentech),其为用于治疗抗TNF难治性类风湿性关节炎(RA)和幼年特发性关节炎(JIA)的重组单克隆IgG1抗人白介素6-受体抗体;ARZERRA™(GlaxoSmithKline/Novartis),其为用于治疗RA的针对CD20分子上的近膜表位的嵌合人单克隆抗体;BENLYSTA™(GlaxoSmithKline),其为用于治疗SLE的结合至并抑制可溶性形式的B-淋巴细胞刺激(BLyS)蛋白的人单克隆IgG1γ;ORENCIA™(Bristol-Myers Squibb),其为结合至抗原呈递细胞上的CD80/86以便抑制T细胞上的CD28的共刺激的CTLA-4IgG1,其是用于治疗RA、JIA及SLE;SIMPONI(Janssen),其为作用于可溶性及膜结合TNF-α上的IgG1单克隆抗体,其是用于治疗RA、牛皮癣关节炎(PsA)及强直性脊柱炎(AS);CIMZIA™(UCB Group),其为用于治疗RA的TNF-α单克隆抗体的聚乙二醇化人源化抗体Fab'片段;西法木单抗(MedImmune),其是为治疗SLE、皮肌炎及多发性肌炎而设计的抗IFN-α单克隆抗体;各种静脉内免疫球蛋白产物,其为用于治疗SLE、全身性硬化及血管炎的来自健康个体的免疫球蛋白的集合;KINERET™(Swedish Oprhan Biovitrum AB)、ILARIS™(Novartis)及ARCALYST™(Regeneron),其为用于治疗RA和cryopyrin相关周期综合征(CAPS)的白介素-1阻断剂。

[0138] 细胞因子

[0139] 在一些情况下,除CC之外,本公开的免疫调节组合物还包含细胞因子。可包括在本公开的免疫调节组合物中的细胞因子包括但不限于白介素、转化生长因子(TGF)、成纤维细胞生长因子(FGF)、血小板衍生生长因子(PDGF)、表皮生长因子(EGF)、集落刺激因子(CSF)、结缔组织活化肽(CTAP)、成骨因子、以及所述生长因子的生物活性类似物、片段及衍生物。合适的细胞因子包括B/T细胞分化因子、B/T细胞生长因子、促有丝分裂细胞因子、趋化性细胞因子、集落刺激因子、血管生成因子、IFN-α、IFN-β、IFN-γ、IL1、IL2、IL3、IL4、IL5、IL6、IL7、IL8、IL9、IL10、IL11、IL12、IL13、IL14、IL15、IL16、IL17、IL18、IL22等、瘦素、肌生长抑制素、巨噬细胞刺激蛋白、血小板衍生生长因子、肿瘤坏死因子(TNF)-α(TNF-α)、TNF-β、神经生长因子(NGF)、CD40L、CD137L/4-1BBL、人淋巴毒素-β、G-CSF、M-CSF、GM-CSF、血小板衍生生长因子(PDGF)、IL-1α、IL1-β、IP-10、PF4、GRO、9E3、促红细胞生成素、内皮抑素、制管张

素、血管内皮生长因子(VEGF)或其任何片段或组合。其它细胞因子包括转化生长因子(TGF)超基因家族的成员，包括β转化生长因子(例如TGF-β1、TGF-β2、TGF-β3)；骨形态发生蛋白(例如BMP-1、BMP-2、BMP-3、BMP-4、BMP-5、BMP-6、BMP-7、BMP-8、BMP-9)；肝素结合生长因子(例如成纤维细胞生长因子(FGF)、表皮生长因子(EGF)、血小板衍生生长因子(PDGF)、胰岛素样生长因子(IGF))；造血生长因子(Flt3)；垂体生长激素或衍生物；生长激素、刺激神经激素、抑制素(例如抑制素A、抑制素B)；分化因子(例如GDF-1)；以及活化素(例如，活化素A、活化素B、活化素AB)。在一些情况下，除CC之外，本公开的免疫调节组合物还包含调节细胞因子的化合物或试剂。

[0140] 佐剂

[0141] 本公开的免疫调节组合物除CC之外还可包含一种或多种佐剂。

[0142] 示例性佐剂包括但不限于：(1)水包油型乳液制剂(有或没有其它特异性免疫刺激剂，如胞壁酰肽(参见下文)或细菌细胞壁组分)，例如像(a)MF59™(WO 90/14837；第10章Vaccine design:the subunit and adjuvant approach，编者Powell&Newman，Plenum Press 1995)，含有5％角鲨烯、0.5％Tween 80和0.5％Span 85(任选含有MTP-PE)，使用微流化器被配制成亚微细粒，(b)SAF，含有10％角鲨烷、0.4％Tween80、5％pluronic-嵌段共聚物L121和thr MDP，被微流化为亚微乳液或涡旋以生成较大粒度的乳液，以及(c)RIBI ™佐剂系统(RAS)(Ribi Immunochem，Hamilton，Mont.)，含有2％角鲨烯、0.2％Tween 80及一种或多种细菌细胞壁组分，如单磷酰脂质A(MPL)、海藻糖双霉菌酸酯(TDM)及细胞壁骨架(CWS)，例如MPL+CWS(Detox ™)；(2)皂角苷佐剂，如可使用QS21或Stimulon™(Cambridge Bioscience，Worcester，Mass.)或由此产生的颗粒，如ISCOMs(免疫刺激复合体)，所述ISCOMS可不含另外的清洁剂，例如WO 00/07621；(3)完全弗氏佐剂(CFA)和不完全弗氏佐剂(IFA)；(4)细胞因子，如白介素(例如，IL-1、IL-2、IL-4、IL-5、IL-6、IL-7、IL-12、IL-15、IL-28等)(WO99/44636)等)、干扰素(例如γ干扰素)、巨噬细胞集落刺激因子(M-CSF)、肿瘤坏死因子(TNF)、集落刺激因子(例如GM-CSF)等；(5)单磷酰脂质A(MPL)或3-O-脱酰化MPL(3dMPL)，例如，GB-2220221、EP-A-0689454，当与肺炎球菌糖一起使用时任选地在实质性缺乏明矾下，例如WO 00/56358；(6)3dMPL与例如QS21和/或水包油乳液的组合，例如EP-A-0835318、EP-A-0735898、EP-A-0761231；(7)包含CpG基序的寡核苷酸(Krieg Vaccine 2000,19,618-622；WO 96/02555、WO 98/16247、WO 98/18810、WO 98/40100、WO 98/55495、WO98/37919及WO 98/52581)，即含有至少一个CG二核苷酸的寡核苷酸，其中胞嘧啶为未甲基化的；(8)聚氧乙烯醚或聚氧乙烯酯，例如WO 99/52549；(9)与辛苯聚醇组合的聚氧乙烯脱水山梨糖醇酯表面活性剂(WO 01/21207)或与至少一种另外的非离子型表面活性剂如辛苯聚醇组合的聚氧乙烯烷基醚或酯表面活性剂(WO 01/21152)；(10)皂角苷和免疫刺激寡核苷酸(例如CpG寡核苷酸)(WO 00/62800)；(11)免疫刺激剂和金属盐颗粒，例如WO 00/23105；(12)皂角苷和水包油型乳液，例如WO 99/11241；(13)皂角苷(例如QS21)+3dMPL+IM2(任选地包括固醇)，例如WO 98/57659；(14)αGalCer及其衍生物；(16)toll样受体(TLR)激动剂、NOD样受体(NLR)激动剂、RIG-I激动剂、C型凝集素受体激动剂及其它病原体识别受体(PRR)激动剂，例如CpG ODN、ISS-ODN、林塔托利(rinatolimod)、聚I:C及其衍生物、鞭毛蛋白、安普利近、咪唑喹啉(imidazoquinaline)(例如咪喹莫特、瑞喹莫德)、胞壁酰二肽；(17)充当免疫刺激剂以提高组合物功效的其它物质。胞壁酰肽包括N-乙酰基-胞壁酰基-L-苏氨

酰基-D-异谷氨酰胺(thr-MDP)、N-25乙酰基-去甲胞壁酰基-L-丙氨酰基-D-异谷氨酰胺(nor-MDP)、N-乙酰胞壁酰基-L-丙氨酰基-D-异谷氨酰胺基-L-丙氨酸-2-(1'-2'-二棕榈酰基-sn-甘油基-3-羟基磷酰氧基)-乙胺MTP-PE)等。在一些情况下,包括适于向人施用的佐剂。

[0143] 其它示例性佐剂包括但不限于:霍乱毒素B亚基、BCG、绿脓假单胞菌外蛋白A、生育酚、HBV核心、大肠埃希氏菌不耐热毒素(如LT-A、LT-B)、百日咳毒素、白喉类毒素、破伤风类毒素、霍乱毒素衍生物(CTA1-DD、CT)、突变的LT和CT、基于铝盐的佐剂(如明矾、磷酸铝、硫酸铝、铝胶)、磷酸钙、高岭土、单磷酰基脂质A(MPL^{R})及其衍生物、吡喃葡萄糖基脂质A、合成脂质A、脂质A模拟物、维生素E、Depovax^{TM}、皂角苷(Quil-A、AS01、AS02(角鲨烯+MPL+QS-21))、AS03、AS04(明矾+MPL^{R})、番茄素(Tomatin)、Protolin、RC-529、Pluronic^{TM}、Monatides、Matrix-M、OM-174、Lipovac、IC-31、细菌/分枝杆菌肽(如KLK、阳离子(聚)肽、抗细菌微生物肽、防卫素、特夫素、抗菌肽)、二肽(如匹多莫德)、贝他定、Hepon(十四肽)、SCV-07(γ-D-谷氨酰基-L-色氨酸)、胸腺素-a、Immunofan、Thymogen、吲哚力西丁(Indolicidin)及其衍生物、聚磷腈(polyphosphagene)及其衍生物、Gellan、核苷酸(单核苷酸、二核苷酸、多核苷酸、环核苷酸)、Eurocine等。

[0144] 除CC之外,本公开的免疫调节组合物还可包含一种或多种粘膜粘着剂,如海藻酸钠、淀粉、凝集素、硫醇化聚合物、GelVac^{TM}、羧甲基纤维素钠、羟丙基甲基纤维素、卡波姆、十六烷基三甲基溴化铵。

[0145] 本公开的免疫调节组合物除CC之外还可包含一种或多种佐剂制剂,如水包油乳液、油包水乳液、纳米乳液、微粒递送系统、脂质体、微球、生物可降解微球、斑块病毒体、蛋白脂质体、蛋白酶体、免疫刺激复合体(ISCOMs、ISCOMATRIX)、微颗粒、纳米颗粒、生物可降解的纳米颗粒、硅纳米颗粒、聚合微米/纳米颗粒、聚合薄片状底物颗粒(PLSP)、微颗粒树脂、纳米脂质体聚合凝胶(nanolipogel)、合成的/生物可降解的及生物相容性半合成或天然聚合物或树枝状聚合物(如PLG、PLGA、PLA、聚己酸内酯、硅聚合物、聚酯、聚二甲基硅氧烷、聚苯乙烯磺酸钠、聚苯乙烯苄基三甲基氯化铵、聚苯乙烯二乙烯基苯树脂、聚磷腈、聚-[二-(羧基乙酰苯氧基)磷腈(PCPP)、聚-(甲基丙烯酸甲酯)、葡聚糖、聚乙烯吡咯烷酮、透明质酸及衍生物、壳聚糖及其衍生物、多糖、δ菊粉多糖、糖脂(合成的或天然的)、脂多糖、一种或多种聚阳离子化合物(如聚氨基酸、聚-(γ-谷氨酸)、聚-精氨酸-HCl、聚-L-赖氨酸、多肽、生物高聚物)、阳离子二甲基二(十八烷基)铵(DDA)、α-半乳糖苷神经酰胺及其衍生物、古细菌脂质及衍生物、内酰胺、gallen、甘油酯、磷脂、螺旋体等或其混合物。

[0146] 本公开的免疫调节组合物除CC之外还可包含一种或多种佐剂制剂,如水包油乳液或油包水乳液,包括可食用油类(如橄榄油、芥子油、植物油、大豆油、矿物油等)。

[0147] 本公开的免疫调节组合物除CC之外还可包含一种或多种表面活性剂和清洁剂(例如,非离子型清洁剂或类脂囊泡)(如Tween-80、聚山梨醇酯80、Span 85、硬脂酪氨酸等)。本公开的免疫调节组合物除CC之外还可包含以上提及的提供贮库效应的组分或佐剂。

[0148] 益生菌

[0149] 本公开的免疫调节组合物除CC之外还可包含一种或多种益生菌。"益生菌"是指含有一个物种(即单一分离株)或纯细菌的组合(即,所需细菌的共培养物)的组合物,并且还可包含任何额外的载体、赋形剂和/或治疗剂,其可向哺乳动物施用以用于恢复微生物群

和/或提供健康益处。益生菌的实例包括但不限于乳杆菌属某种、双歧杆菌属某种(Bifidobacteria sp.)、布拉酵母菌(Saccharomyces boulardii)、链球菌属某种(Streptococcus sp.)、屎肠球菌(Enterococcusfaecium)、凝结芽孢杆菌(Bacillus coagulans)、梭菌属某种(Faecalibacterium sp.)等。

[0150] 益生元

[0151] 本公开的免疫调节组合物除CC之外还可包含一种或多种益生元。如本文所用,术语“益生元”是指并非由摄取它们的哺乳动物所消化但是作为用于微生物群(特别是肠道微生物群)的生长或活性的基质的营养增补剂。许多益生元为碳水化合物,例如多糖和低聚糖,但该定义不排除非碳水化合物。最普遍形式的益生元在营养学上被归类为可溶性纤维。益生元可提供在胃肠道微生物群的组成和/或活性方面的变化。“益生元”还指的是含有无活力的食物组分的组合物,所述食物组分特别是由被认为具有积极价值的固有细菌(如双歧杆菌属、乳杆菌属等)在体内代谢。益生元的实例包括但不限于果糖、木糖、大豆、葡萄糖、甘露糖等。

[0152] 微生物群

[0153] 术语“微生物群”、“微生物组”、“共生菌”或“共生体”可互换使用并且是指在个体中的不同位置(如肠、皮肤、唾液、结肠、阴道、肺等)处的微生物群体(细菌、病毒、真菌、寄生虫)。微生物群的平衡失调与若干自身免疫和炎性疾病的病因或发病有关。本公开的免疫调节组合物除CC之外还可包含个体的微生物群的成员,如拟杆菌门(Bacteroidetes)、变形菌门(Proteobacteria)、厚壁菌门(Firmicutes)、疣微菌门(Verrucomicrobia)、拟杆菌目(Bacteriodales)、肠杆菌目(Enterobacteriales)、梭菌属等。微生物群的成员的其它实例是已知的或将为本领域技术人员显而易见。参见,美国专利申请号2014/0010844。参见,Howarth和Wang,Nutrients.2013,5(1):58-81,关于内源性微生物群、益生菌及它们的生物制品的作用的说明。因此,本发明组合物可用于建立、调节、调控或维持平衡的微生物群。微生物组的成员可以是自体、同种异体及异种来源的、野生型、活的、灭活的、热杀的、突变的、减毒的和/或遗传工程化的。

[0154] 治疗性病原体

[0155] 除CC之外,本公开的免疫调节组合物还可包含治疗性致病细菌、病毒、真菌等,如李斯特氏菌属、酵母菌属、埃希氏菌属、沙门氏菌属、葡萄球菌属(Staphylococcus)、克雷伯氏菌属(Klebsiella)、痘病毒、腺病毒、溶瘤病毒。治疗性微生物致病体的其它实例是已知的或将为本领域技术人员显而易见。参见,美国专利申请号2014/0010844。治疗性病原体可为野生型、活的、灭活的、热杀的、突变的、减毒的和/或基因工程化的。

[0156] 治疗剂

[0157] 本公开的免疫调节组合物除CC之外还可包含一种或多种治疗剂。治疗剂的实例是已知的或将为本领域技术人员显而易见。在本文“方法”章节中提供治疗剂的非限制性实例,包括抗炎剂、抗增殖剂、免疫抑制剂、抗组胺剂、免疫调控剂、免疫调节剂、抗代谢剂、抗过敏剂、细胞毒性剂、抗蠕虫剂、抗血管生成剂、抗微生物剂(如抗病毒剂、抗细菌剂、抗寄生虫剂、抗疟疾剂、抗原生动物剂)、治疗性肽等。

[0158] 方法

[0159] 本公开提供调节个体中的免疫应答的方法,所述方法包括向所述个体施用有效量

的本公开的免疫调节组合物。本公开提供降低个体中不希望的免疫应答的方法，所述方法包括向所述个体施用有效量的本公开的免疫降低组合物。本公开提供减轻个体中的炎症的方法，所述方法包括向所述个体施用有效量的本公开的免疫降低组合物。本公开提供治疗个体中的自身免疫病症的方法，所述方法包括向所述个体施用有效量的本公开的免疫调节组合物。本公开提供治疗个体中的过敏(过敏性疾病)的方法，所述方法包括向所述个体施用有效量的本公开的免疫调节组合物。本公开提供治疗个体的代谢疾病的方法，所述方法包括向所述个体施用有效量的本公开的免疫调节组合物。本公开提供治疗个体的神经障碍的方法，所述方法包括向所述个体施用有效量的本公开的免疫调节组合物。本公开提供提高个体中的治疗性治疗的功效和/或降低其毒性的方法，所述方法包括向所述个体施用有效量的本公开的免疫调节组合物。本公开提供治疗、恢复或纠正与个体中的微生物组失衡有关的疾病或医学病状的方法，所述方法包括向所述个体施用有效量的本公开的免疫调节组合物。本公开提供治疗、恢复或纠正个体的菌群失调的方法，所述方法包括向所述个体施用有效量的本公开的免疫调节组合物。

[0160] 本公开还提供一种调节树突细胞的方法，所述方法包括：a)使从个体处获得的树突细胞(DC)与包含以下的组合物接触：i)新月柄杆菌；和/或ii)抗原；所述接触步骤是在体外的，以及调节DC上的抗原呈递，由此生成调节的DC群。然后可将调节的DC群向DC由其获得的个体施用。

[0161] 在一些情况下，各种免疫细胞可从淋巴组织、外周血液、器官及组织处获得和/或可从由骨髓或各种器官处获得的干细胞分化而来。

[0162] 本公开还提供一种诱导干细胞的增殖、分化和/或调节的方法，所述方法包括使从个体处获得的干细胞与包含新月柄杆菌的组合物接触。干细胞与CC的接触造成干细胞的增殖、分化和/或调节，由此生成扩增的、分化的和/或调节的细胞群。然后可将扩增的、分化的和/或调节的细胞群向干细胞由其获得的个体施用。

[0163] 本公开还提供一种产生调控性淋巴细胞如NK、NKT、γδT细胞、ILC、T细胞及B细胞的方法，所述方法包括：a)使从个体处获得的淋巴细胞(NK、NKT、γδT细胞、ILC、T细胞、B细胞)在抗原呈递细胞存在或不存在下与包含以下的组合物接触：i)新月柄杆菌；和/或ii)抗原。淋巴细胞与CC的接触产生调控性淋巴细胞，由此生成调控性淋巴细胞群。然后可将调控性淋巴细胞群向淋巴细胞由其获得的个体施用。

[0164] 调节免疫应答的方法

[0165] 本公开提供调节个体中的免疫应答的方法，所述方法包括向所述个体施用有效量的本公开的免疫调节组合物。本公开提供降低个体中不希望的免疫应答的方法，所述方法包括向所述个体施用有效量的本公开的免疫降低组合物。本公开提供减轻个体中的炎症的方法，所述方法包括向所述个体施用有效量的本公开的免疫降低组合物。本公开提供治疗个体中的自身免疫病症的方法，所述方法包括向所述个体施用有效量的本公开的免疫调节组合物。本公开提供治疗个体中的过敏(过敏性疾病)的方法，所述方法包括向所述个体施用有效量的本公开的免疫调节组合物。

[0166] 在一些情况下，免疫应答为体液免疫应答。在一些情况下，本公开提供调节个体中的体液免疫应答的方法，所述方法包括向所述个体施用有效量的本公开的免疫调节组合物。在一些情况下，免疫调节组合物不包括任何另外的抗原(除CC上存在的抗原以外)。在一

些情况下，免疫调节组合物包含抗原(例如，除CC上存在的抗原以外的抗原)。如上所述，合适的抗原包括自身抗原和过敏原。

[0167] 在一些情况下，免疫应答为细胞免疫应答。在一些情况下，本公开提供调节个体中的细胞免疫应答的方法，所述方法包括向所述个体施用有效量的本公开的免疫调节组合物。在一些情况下，免疫调节组合物不包括任何另外的抗原(除CC上存在的抗原以外)。在一些情况下，免疫调节组合物包含抗原(例如，除CC上存在的抗原以外的抗原)。如上所述，合适的抗原包括自身抗原和过敏原。

[0168] 在一些情况下，免疫应答包括调节B细胞的数量。在一些情况下，本发明方法包括向有此需要的个体施用有效量的免疫调节组合物，其中免疫调节组合物的有效量为当以单剂量或多剂量向个体施用时有效调节(例如减少)个体中的B细胞数量的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中的B细胞数量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中的B细胞数量至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍或大于10倍的量。在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中的抗原特异性B细胞数量的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中的抗原特异性B细胞数量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中的抗原特异性B细胞数量至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍或大于10倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中的抗原特异性B细胞数量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中的抗原特异性B细胞数量至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中的自身抗原特异性B细胞数量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中的自身抗原特异性B细胞数量至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0169] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如降低)个体中的B细胞活化的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中的B细胞活化水平相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如降低)个体中的B细胞活化至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中的B细胞活化水平相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效降低个体中的B细胞活化至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0170] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时

有效调节(例如减少)个体中对给定抗原有特异性的抗体的量的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中对给定抗原有特异性的抗体的量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中对所述抗原有特异性的抗体的量至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%、至少100%(或2倍)、至少2.5倍、至少5倍、至少10倍或大于10倍的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中对给定抗原有特异性的抗体的量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中对所述抗原有特异性的抗体的量至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%或大于75%的量。

[0171] 在一些情况下,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中一种或多种细胞因子产生的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中一种或多种细胞因子产生的量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中所述一种或多种细胞因子的产生至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%、至少100%(或2倍)、至少2.5倍、至少5倍、至少10倍或大于10倍的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中一种或多种细胞因子的产生相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中所述一种或多种细胞因子的产生至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%或大于75%的量。在其它情况下,与在不存在免疫调节组合物治疗下个体中GM-CSF的量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中GM-CSF的产生至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%、至少100%(或2倍)、至少2.5倍、至少5倍、至少10倍或大于10倍的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中GM-CSF的量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中GM-CSF的产生至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%或大于75%的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中IL-22的量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中IL-22的产生至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%、至少100%(或2倍)、至少2.5倍、至少5倍、至少10倍或大于10倍的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中IL-22的量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中IL-22的产生至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%或大于75%的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中干扰素(IFN)-α或IFN-β或IFN-γ的量相比,本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中IFN-α和/或IFN-β和/或IFN-γ的产生至少10%、至少15%、至少20%、至少25%、至少30%、至少35%、至少40%、至少45%、至少50%、至少75%、至少100%(或2倍)、至少2.5倍、至少5倍、至少10倍或大于10倍的量。例如,在一些情况下,与在不存在免疫调节组合物治疗下个体中干扰素(IFN)-α

和/或IFN-β和/或IFN-γ的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中干扰素(IFN)-α和/或IFN-β和/或IFN-γ的产生至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中IL-17A、IL-2、IL-10、IL-6或TNF-α的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中IL-17A、IL-2、IL-10、IL-6或TNF-α的一种或多种的产生至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍或大于10倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中IL-17A、IL-2、IL-10、IL-6或TNF-α的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中IL-17A、IL-2、IL-10、IL-6或TNF-α的一种或多种的产生至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中IL-6的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中IL-6的产生至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中IL-1β的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中IL-1β的产生至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。在一些情况下，与在不存在免疫调节组合物治疗下个体中TGF-β的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效提高个体中TGF-β的水平至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍或大于10倍的量。

[0172] 在一些情况下，与在不存在免疫调节组合物治疗下个体中细胞因子、趋化因子或淋巴毒素如但不限于GM-CSF、IL-2、IL-22、干扰素、IL-1β、TGF-β、IL-17A、IL-2、IL-10、IL-6、IL-5、IL-13、TNF-α、IL-9、IL-28、KC/IL-8、MIP-1α、LTα4等的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如增加、减少或平衡)个体中一种或多种细胞因子、趋化因子或淋巴毒素如但不限于GM-CSF、IL-2、IL-22、干扰素、IL-1β、TGF-β、IL-17A、IL-2、IL-10、IL-6、IL-5、IL-13、TNF-α、IL-9、IL-28、KC/IL-8、MIP-1α、LTα4等的产生至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍或大于10倍的量。

[0173] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如降低)个体中的Th1应答的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中的Th1应答水平相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如降低)个体中的Th1应答至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体

中的Th1应答相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效降低个体中的Th1应答至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0174] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中$CD4^+$T细胞的数量和/或活性的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中$CD4^+$T细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中$CD4^+$T细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中抗原特异性$CD4^+$T细胞的数量和/或活性的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中抗原特异性$CD4^+$T细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中抗原特异性$CD4^+$T细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中$CD4^+$T细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中$CD4^+$T细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中抗原特异性$CD4^+$T细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中抗原特异性$CD4^+$T细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0175] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中$CD8^+$T细胞的数量和/或活性的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中$CD8^+$T细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中$CD8^+$T细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中抗原特异性$CD8^+$T细胞的数量和/或活性的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中抗原特异性$CD8^+$T细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中抗原特异性$CD8^+$T细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在

一些情况下，与在不存在免疫调节组合物治疗下个体中$CD8^+$T的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中$CD8^+$T的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中抗原特异性$CD8^+$T的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中抗原特异性$CD8^+$T的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中自身抗原特异性$CD8^+$T细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中自身抗原特异性$CD8^+$T细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0176] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中溶细胞性T细胞的数量和/或活性的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中溶细胞性T细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中溶细胞性T细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中抗原特异性溶细胞性T细胞的数量和/或活性的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中抗原特异性溶细胞性T细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中抗原特异性溶细胞性T细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中溶细胞性T细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中溶细胞性T细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中抗原特异性溶细胞性T细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中抗原特异性溶细胞性T细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0177] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节个体中自然杀伤(NK)细胞、NKT细胞、γδT细胞、ILC、巨噬细胞和树突细胞(DC)中的一种或多种的数量和/或活性的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中NK细胞、NKT细胞、γδT细胞、ILC、巨噬细胞和DC中的一种或多种的数量和/或活

性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节个体中NK细胞、NKT细胞、γδT细胞、ILC、巨噬细胞和DC中的一种或多种的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中NK细胞、NKT细胞、γδT细胞、ILC、巨噬细胞和DC的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节个体中NK细胞、NKT细胞、γδT细胞、ILC、巨噬细胞和DC中的一种或多种的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0178] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效增加、减少或平衡个体中调控性细胞的数量和/或功能的量。Treg(调控性T细胞)为$CD4^+$或$CD8^+$，并且还可为$FoxP3^+$。Treg还可由其它标记如PD-1、CTLA-4等定义。调控性细胞还可包含其它先天性细胞，如NK、NKT、γδT细胞、ILC和DC、及B淋巴细胞。NK和NKT也可为$FoxP3^+$并且也可由其它标记如PD-1定义。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中调控性细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节个体中调控性细胞的数量至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中的调控性细胞数量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效增加个体中的调控性细胞数量至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0179] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中Th17细胞的数量和/或活性的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中Th17细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中Th17细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中抗原特异性Th17细胞的数量和/或活性的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中抗原特异性Th17细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中抗原特异性Th17细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中Th17细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中Th17细胞

的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中抗原特异性Th17细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中抗原特异性Th17细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0180] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中Th22细胞的数量和/或活性的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中Th22细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中Th22细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中抗原特异性Th22细胞的数量和/或活性的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中抗原特异性Th22细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中抗原特异性Th22细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中Th22细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中Th22细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中抗原特异性Th22细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中抗原特异性Th22细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0181] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节个体中TH9细胞的数量和/或活性的量。如本文所用，“调节TH9细胞的数量和/或活性”是指增加、减少或平衡TH9细胞的数量和/或活性。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中TH9细胞的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节个体中TH9细胞的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。

[0182] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如降低)个体中先天性和/或适应性(包括细胞和体液两者)免疫应答的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中一种或多种先天性或适应性

免疫细胞和/或其效应子功能的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)个体中先天性和/或适应性免疫细胞和/或其效应子功能的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中先天性和/或适应性免疫细胞和/或其效应子功能的数量和/或活性相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中先天性和/或适应性免疫细胞和/或其效应子功能的数量和/或活性至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0183] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效诱导和/或加强个体中先天性和/或适应性免疫细胞中的细胞凋亡以免发生不希望的炎症的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中一种或多种先天性或适应性免疫细胞的数量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效诱导和/或加强个体中先天性和/或适应性免疫细胞中的细胞凋亡至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。

[0184] 在一些情况下，本公开的免疫调节组合物包含CC和抗原。当本公开的免疫调节组合物包含CC和抗原时，在一些情况下，与在不存在免疫调节组合物治疗下针对抗原的免疫应答相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如降低)针对抗原的免疫应答至少约10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，当抗原为与自身抗原或过敏原相关或来源于自身抗原或过敏原的抗原时，与在不存在免疫调节组合物治疗下针对抗原的免疫应答相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如降低)针对抗原的免疫应答至少约10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，当免疫调节组合物包含单独或以组合形式的CC、抗原、自身抗原或过敏原时，在一些情况下，与在不存在免疫调节组合物治疗下个体中针对抗原的免疫应答相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效降低个体中针对抗原的免疫应答至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0185] 免疫应答可为体液免疫应答，例如B细胞或抗体免疫应答。因此，例如，在一些情况下，当抗原为与自身抗原或过敏原相关或来源于自身抗原或过敏原的抗原时，与在不存在免疫调节组合物治疗下针对抗原的B细胞应答相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如降低)针对抗原的B细胞应答至少约10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、

至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中针对抗原的B细胞应答相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效降低个体中针对抗原的B细胞应答至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。例如，在一些情况下，当抗原为与自身抗原或过敏原相关或来源于自身抗原或过敏原的抗原时，与在不存在免疫调节组合物治疗下对抗原有特异性的抗体的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如减少)对抗原有特异性的抗体的量至少约10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中对抗原有特异性的抗体的量相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效减少个体中对抗原有特异性的抗体的量至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0186] 免疫应答可为细胞免疫应答，例如T细胞免疫应答。因此，例如，在一些情况下，当抗原为与自身抗原或过敏原相关或来源于自身抗原或过敏原的抗原时，与在不存在免疫调节组合物治疗下针对抗原的T细胞应答相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效调节(例如降低)针对抗原的T细胞应答至少约10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中针对抗原的T细胞应答相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效降低个体中针对抗原的T细胞应答至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。在一些情况下，免疫应答为体液免疫应答和细胞免疫应答。

[0187] 在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效标准化病理免疫应答的一种或多种血清标记的水平的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下个体中CHOL、GLU、GLOB、ALT、AST、TP、PHOS、TRIG、URIC、CK、TBIL或尿素的水平相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效标准化一种或多种血清标记(这些标记包括但不限于胆固醇(CHOL)、葡萄糖(GLU)、球蛋白(GLOB)、丙氨酸转氨酶(ALT)、天冬氨酸转氨酶(AST)、总磷酸盐(TP)、总胆红素(TBIL)、磷酸盐(PHOS)、甘油三酯(TRIG)、尿酸(URIC)、肌酸激酶(CK)和尿素)的水平至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％或大于75％的量。

[0188] 佐剂

[0189] 在一些实施方案中，本发明方法包括施用本发明的免疫调节组合物，其中所述免疫调节组合物包含CC和一种或多种佐剂。

[0190] 示例性佐剂包括但不限于：(1)水包油型乳液制剂(有或没有其它特异性免疫刺激

剂，如胞壁酰肽(参见下文)或细菌细胞壁组分)，例如像(a)MF59™(WO 90/14837；第10章Vaccine design:the subunit and adjuvant approach，编者Powell&Newman，Plenum Press 1995)，含有5％角鲨烯、0.5％Tween 80和0.5％Span 85(任选含有MTP-PE)，使用微流化器被配制成亚微细粒，(b)SAF，含有10％角鲨烷、0.4％Tween80、5％pluronic-嵌段聚合物L121和thr MDP，被微流化为亚微乳液或涡旋以生成较大粒度的乳液，以及(c)RIBI ™佐剂系统(RAS)(Ribi Immunochem，Hamilton，Mont.)，含有2％角鲨烯、0.2％Tween 80及一种或多种细菌细胞壁组分，如单磷酰脂质A(MPL)、海藻糖双霉菌酸酯(TDM)及细胞壁骨架(CWS)，例如MPL+CWS(Detox ™)；(2)皂角苷佐剂，如可使用QS21或Stimulon™(Cambridge Bioscience，Worcester，Mass.)或由此产生的颗粒，如ISCOM(免疫刺激复合体)，所述ISCOMS可不含另外的清洁剂，例如WO 00/07621；(3)完全弗氏佐剂(CFA)和不完全弗氏佐剂(IFA)；(4)细胞因子，如白介素(例如，IL-1、IL-2、IL-4、IL-5、IL-6、IL-7、IL-12、IL-15、IL-28等)(WO99/44636)等)、干扰素(例如γ干扰素)、巨噬细胞集落刺激因子(M-CSF)、肿瘤坏死因子(TNF)、集落刺激因子(例如GM-CSF)等；(5)单磷酰脂质A(MPL)或3-O-脱酰化MPL(3dMPL)，例如，GB-2220221、EP-A-0689454，当与肺炎球菌糖一起使用时任选地在实质性缺乏明矾下，例如WO 00/56358；(6)3dMPL与例如QS21和/或水包油乳液的组合，例如EP-A-0835318、EP-A-0735898、EP-A-0761231；(7)包含CpG基序的寡核苷酸(Krieg Vaccine 2000，19，618-622；WO 96/02555、WO 98/16247、WO 98/18810、WO 98/40100、WO 98/55495、WO 98/37919及WO 98/52581)，即含有至少一个CG二核苷酸的寡核苷酸，其中胞嘧啶为未甲基化的；(8)聚氧乙烯醚或聚氧乙烯酯，例如WO 99/52549；(9)与辛苯聚醇组合的聚氧乙烯脱水山梨糖醇酯表面活性剂(WO 01/21207)或与至少一种非离子型表面活性剂如辛苯聚醇组合的聚氧乙烯烷基醚或酯表面活性剂(WO 01/21152)；(10)皂角苷和免疫刺激寡核苷酸(例如CpG寡核苷酸)(WO 00/62800)；(11)免疫刺激剂和金属盐颗粒，例如WO 00/23105；(12)皂角苷和水包油型乳液，例如WO 99/11241；(13)皂角苷(例如QS21)+3dMPL+IM2(任选地包括固醇)，例如WO 98/57659；(14)αGalCer及其衍生物；(16)toll样受体(TLR)激动剂、NOD样受体(NLR)激动剂、RIG-I激动剂、C型凝集素受体激动剂及其它病原体识别受体(PRR)激动剂，例如CpG ODN、ISS-ODN、rinatolimod、聚I:C及其衍生物、鞭毛蛋白、安普利近、咪唑喹啉(imidazoquinaline)(例如咪喹莫特、瑞喹莫德)、胞壁酰二肽；(17)充当免疫刺激剂以提高组合物功效的其它物质。胞壁酰肽包括N-乙酰基-胞壁酰基-L-苏氨酰基-D-异谷氨酰胺(thr-MDP)、N-25乙酰基-去甲胞壁酰基-L-丙氨酰基-D-异谷氨酰胺(nor-MDP)、N-乙酰胞壁酰基-L-丙氨酰基-D-异谷氨酰胺基-L-丙氨酸-2-(1'-2'-二棕榈酰基-sn-甘油基-3-羟基磷酰氧基)-乙胺MTP-PE)等。在一些情况下，包括适于向人施用的佐剂。

[0191] 其它示例性佐剂包括但不限于：霍乱毒素B亚基、BCG、绿脓假单胞菌(Pseudomonas aeruginosa)外蛋白A、生育酚、HBV核心、大肠埃希氏菌不耐热毒素(如LT-A、LT-B)、百日咳毒素、白喉类毒素、破伤风类毒素、霍乱毒素衍生物(CTA1-DD、CT)、突变的LT和CT、基于铝盐的佐剂(如明矾、磷酸铝、硫酸铝、铝胶)、磷酸钙、高岭土、单磷酰基脂质A(MPL^{R})及其衍生物、吡喃葡萄糖基脂质A、合成脂质A、脂质A模拟物、维生素E、Depovax™、皂角苷(Quil-A、AS01、AS02(角鲨烯+MPL+QS-21))、AS03、AS04(明矾+MPL^{R})、番茄素(Tomatin)、Protolin、RC-529、Pluronic™、Monatides、Matrix-M、OM-174、Lipovac、IC-31、细菌/分枝杆菌肽(如KLK、阳离子(聚)肽、抗细菌微生物肽、防卫素、特夫素、抗菌肽)、二肽(如匹多莫德)、贝他

定、Hepon(十四肽)、SCV-07(γ-D-谷氨酰基-L-色氨酸)、胸腺素-a、Immunofan、Thymogen、Indolicidin及其衍生物、聚磷腈及其衍生物、Gellan、核苷酸(单核苷酸、二核苷酸、多核苷酸、环核苷酸)、Eurocine等。

[0192] 组合疗法

[0193] 在一些实施方案中,本发明方法涉及施用本发明的免疫调节组合物作为单一疗法,例如,仅施用本发明的免疫调节组合物,而不共同施用任何其它治疗剂。在其它实施方案中,本发明治疗方法为一种组合疗法,其包括施用:a)本发明的免疫调节组合物;和b)至少一种另外的治疗剂(或所述治疗剂的药学上可接受的盐、前药、前药的盐、立体异构体、互变异构体等),其中免疫调节组合物和至少一种另外的治疗剂是以有效调节免疫应答的组合量来施用。合适的另外的治疗剂描述如下。

[0194] 本发明的组合疗法可包括:a)在同一制剂或单独的制剂中同时施用免疫调节组合物和至少一种另外的治疗剂;b)在施用免疫调节组合物的约5分钟至约4周内施用至少一种另外的治疗剂,例如,在施用免疫调节组合物的以下时段内施用至少一种另外的治疗剂:约5分钟至约15分钟、约15分钟至约30分钟、约30分钟至约60分钟、约1小时至约2小时、约2小时至约4小时、约4小时至约8小时、约8小时至约12小时、约12小时至约24小时、约24小时至约2天、约2天至约4天、约4天至约7天、约1周至约2周、或约2周至约4周。

[0195] 在一些实施方案中,将至少一种另外的治疗剂与免疫调节组合物共配制。在其它实施方案中,将至少一种另外的治疗剂和免疫调节组合物单独配制。

[0196] 在一些实施方案中,免疫调节组合物和至少一种另外的治疗剂的有效量为协同量。如本文所用,本发明的免疫调节组合物和另外的(例如第二)治疗剂的“协同组合”或“协同量”为在疾病的治疗性或预防性治疗上比可仅从以下的相加性组合所预测或预期的治疗结果的渐进改善更有效的组合或量:(i)当以与单一疗法相同的剂量施用时免疫调节组合物的治疗性或预防性益处及(ii)当以与单一疗法相同的剂量施用时另外的治疗剂的治疗性或预防性益处。

[0197] 本发明的组合疗法可包括:施用免疫调节组合物和至少一种另外形式的疗法,如放射疗法(包括放射性同位素,如^{125}I、锶-89、^{32}P、α-放射性同位素、β-放射同位素等)、光动力疗法、激光疗法、天然产物疗法、营养疗法、细胞疗法、益生元疗法、益生菌疗法、共生疗法、副益生菌疗法等,在相同或不同的时间下给予。

[0198] 本发明的组合疗法可包括:施用免疫调节组合物和至少一种另外形式的疗法,如个体的微生物群的一个或多个成员,如拟杆菌门、变形菌门、厚壁菌门、疣微菌门、拟杆菌目、肠杆菌目、梭菌属、VSL#3等,在相同或不同的时间下给予。因此,本发明可用于建立、调节、调控或维持平衡的微生物群。微生物组的成员可为野生型、活的、灭活的、热杀的、突变的、减毒的和/或基因工程化的。

[0199] 本发明的组合疗法可包括:施用免疫调节组合物和至少一种另外形式的疗法,如益生菌的一个或多个成员。

[0200] 本发明的组合疗法可包括:施用免疫调节组合物和至少一种另外形式的疗法,如治疗性致病细菌、病毒、真菌等的一个或多个成员,如李斯特氏菌属、酵母属、埃希氏菌属、沙门氏菌属、葡萄球菌属、克雷伯氏菌属、痘病毒、腺病毒、溶瘤细胞病毒。治疗性病原体可为野生型、突变的、减毒的和/或基因工程化的。治疗性病原体的成员可为野生型、活的、灭

活的、热杀的、突变的、减毒的和/或基因工程化的。

[0201] 在一些实施方案中，有效量的免疫调节组合物可在异源或同源初次-加强疫苗、免疫疗法和/或化疗方案中施用。

[0202] 本发明的组合疗法可包括：施用免疫调节组合物和治疗性疫苗。

[0203] 本发明的组合疗法可包括：施用免疫调节组合物和治疗性抗体。例如，在一些实施方案中，本发明方法包括：a)施用本公开的免疫调节组合物；及b)施用至少一种抗体。CC和抗体可在同一制剂中或在单独的制剂中。CC和抗体可同时或在不同的时间施用。合适的抗体包括针对癌抗原或致病抗原的抗体(例如，治疗性抗体、单克隆抗体、双特异性抗体、化学免疫缀合抗体、放射免疫缀合抗体、抗体-细胞因子融合蛋白、抗体-抗原融合蛋白、抗体-抗毒素融合蛋白等)。合适的抗体包括但不限于针对共刺激或共抑制分子(CD28、CD40、ICOS、CD137、OX40、CD137、CD227、CTLA-4、PD-1、KIR、TCR、PDL1、LAG3、TIM3、VISTA等)的抗体；及其它治疗性抗体。合适抗体的非限制性实例包括但不限于阿达木单抗、贝伐单抗、英夫利昔单抗、阿昔单抗、阿来组单抗、巴匹珠单抗、巴利昔单抗、贝利单抗、巴列津单抗、布罗达单抗、康纳单抗、塞妥珠单抗、西妥昔单抗、西他土珠(conatumumab)、地诺单抗、依库珠单抗、etrolizumab、吉妥单抗奥佐米星、格里木单抗、替伊莫单抗、拉贝珠单抗、马帕妥木单抗、马妥珠单抗、美泊利单抗、莫维珠单抗、莫罗单抗-CD3、那他珠单抗、尼妥珠单抗、奥法木单抗、奥马佐单抗、奥戈伏单抗、帕利珠单抗、帕尼单抗、pemtumornab、帕妥珠单抗、兰尼单抗、利妥昔单抗、罗维珠单抗、托珠单抗、托西莫单抗、曲妥单抗、优特克单抗、维多珠单抗、扎鲁木单抗及扎木单抗。

[0204] 可与本公开的免疫调节组合物组合使用的治疗性和预防性抗体的非限制性实例包括MDX-010(Medarex,N.J.)，其为用于治疗前列腺癌的人源化抗CTLA-4抗体；SYNAGIS™(MedImmune,Md.)，其为用于治疗RSV感染的人源化抗呼吸道合胞病毒(RSV)单克隆抗体；及HERCEPTIN™(曲妥单抗)(Genentech,Calif.)，其为用于治疗转移性乳腺癌的人源化抗HER2单克隆抗体。其它实例为人源化抗CD18F(ab')$_2$(Genentech)；CDP860，其为人源化抗CD18F(ab')$_2$(Celltech,UK)；PRO542，其为与CD4融合的抗HIV gp120抗体(Progenics/Genzyme Transgenics)；奥司他韦，其为人抗乙型肝炎病毒抗体(Protein Design Lab/Novartis)；PROTOVIR™，其为人源化抗CMV IgGI抗体(Protein Design Lab/Novartis)；MAK-195(SEGARD)，其为鼠抗TNF-αF(ab')$_2$(Knoll Pharma/BASF)；IC14，其为抗CD14抗体(ICOS Pharm)；人源化抗VEGF IgG1抗体(Genentech)；OVAREX™，其为鼠抗CA 125抗体(Altarex)；PANOREX™，其为鼠抗17-IA细胞表面抗原IgG2a抗体(Glaxo Wellcome/Centocor)；BEC2，其为鼠抗独特型(GD3表位)IgG抗体(ImClone System)；IMC-C225，其为嵌合抗EGFR IgG抗体(ImClone System)；VITAXIN™，其为人源化抗αVβ3整联蛋白抗体(Applied Molecular Evolution/MedImmune)；Campath 1H/LDP-03，其为人源化抗CD52IgG1抗体(Leukosite)；Smart M195，其为人源化抗CD33IgG抗体(Protein Design Lab/Kanebo)；RITUXAN™，其为嵌合抗CD20IgG1抗体(IDEC Pharm/Genentech,Roche/Zettyaku)；LYMPHOCIDE™，其为人源化抗CD22IgG抗体(Immunomedics)；Smart ID10，其为人源化抗HLA抗体(Protein Design Lab)；ONCOLYM™(Lym-1)，其为放射性同位素标记的鼠抗HLA诊断试剂抗体(Techniclone)；ABX-IL8，其为人抗IL8抗体(Abgenix)；抗CD11a，其为人源化IgG1抗体(Genentech/Xoma)；ICM3，其为人源化抗ICAM3抗体(ICOS Pharm)；IDEC-114，其为灵长类动物源化抗CD80抗体

(IDEC Pharm/Mitsubishi);ZEVALIN™,其为放射性同位素标记的鼠抗CD20抗体(IDEC/Schering AG);IDEC-131,其为人源化抗CD40L抗体(IDEC/Eisai);IDEC-151,其为灵长类动物源化抗CD4抗体(IDEC);IDEC-152,其为灵长类动物源化抗CD23抗体(IDEC/Seikagaku);SMART抗CD3,其为人源化抗CD3IgG(Protein Design Lab);5G1.1,其为人源化抗补体因子5(C5)抗体(Alexion Pharm);D2E7,其为人源化抗TNF-α抗体(CAT/BASF);CDP870,其为人源化抗TNF-αFab片段(Celltech);IDEC-151,其为灵长类动物源化抗CD4IgG1抗体(IDEC Pharm/SmithKline Beecham);MDX-CD4,其为人抗CD4IgG抗体(Medarex/Eisai/Genmab);CDP571,其为人源化抗TNF-αIgG4抗体(Celltech);LDP-02,其为人源化抗α4β7抗体(LeukoSite/Genentech);OrthoClone OKT4A,其为人源化抗CD4IgG抗体(Ortho Biotech);ANTOVA™,其为人源化抗CD40L IgG抗体(Biogen);ANTEGREN™,其为人源化抗VLA-4IgG抗体(Elan);MDX-33,其为人抗CD64(FcγR)抗体(Medarex/Centeon);SCH55700,其为人源化抗IL-5IgG4抗体(Celltech/Schering);SB-240563和SB-240683,其分别为人源化抗IL-5和IL-4抗体(SmithKline Beecham);rhuMab-E25,其为人源化抗IgE IgG1抗体(Genentech/Norvartis/Tanox Biosystems);ABX-CBL,其为鼠抗CD-147IgM抗体(Abgenix);BTI-322,其为大鼠抗CD2IgG抗体(MedImmune/Bio Transplant);Orthoclone/OKT3,其为鼠抗CD3IgG2a抗体(ortho Biotech);SIMULECT™,其为嵌合抗CD25IgG1抗体(Novartis Pharm);LDP-01,其为人源化抗β_2-整联蛋白IgG抗体(LeukoSite);抗LFA-1,其为鼠抗CD18F(ab').sub.2(Pasteur-Merieux/Immunotech);CAT-152,其为人抗TGF-β_2抗体(Cambridge Ab Tech);以及Corsevin M,其为嵌合抗因子VII抗体(Centocor)。以上列出的免疫反应剂以及任何其它免疫反应剂可根据本领域技术人员已知的任何方案来施用,包括由免疫反应剂的供应商所推荐的方案。

[0205] 可与本公开的免疫调节组合物组合使用的治疗性和预防性抗体的其它实例包括阿达木单抗和英利昔单抗(Remicade);ACTEMRA™(Genentech),其为用于治疗抗TNF难治性RA和幼年特发性关节炎(JIA)的重组单克隆IgG1抗人白介素6-受体抗体;ARZERRA™(GlaxoSmithKline/Novartis),其为用于治疗RA的针对CD20分子上的近膜表位的嵌合人单克隆抗体;BENLYSTA™(GlaxoSmithKline),其为用于治疗SLE的结合至并抑制可溶性形式的B-淋巴细胞刺激(BLyS)蛋白的人单克隆IgG1γ;ORENCIA™(Bristol-Myers Squibb),其为结合至抗原呈递细胞上的CD80/86以便抑制T细胞上的CD28的共刺激的CTLA-4IgG1,其是用于治疗RA、JIA及SLE;SIMPONI(Janssen),其为作用于可溶性及膜结合TNF-α上的IgG1单克隆抗体,其是用于治疗RA、牛皮癣关节炎(PsA)及强直性脊柱炎(AS);CIMZIA™(UCB Group),其为用于治疗RA的TNF-α单克隆抗体的聚乙二醇化人源化抗体Fab'片段;西法木单抗(MedImmune),其是为治疗SLE、皮肌炎及多发性肌炎而设计的抗IFN-α单克隆抗体;各种静脉内免疫球蛋白产物,其为用于治疗SLE、全身性硬化及血管炎的来自健康个体的免疫球蛋白的集合;KINERET™(Swedish Oprhan Biovitrum AB)、ILARIS™(Novartis)及ARCALYST™(Regeneron),其为用于治疗RA和cryopyrin相关周期综合征(CAPS)的白介素-1阻断剂。

[0206] 本发明的组合疗法可包括:施用本公开的免疫调节组合物和一种或多种细胞因子。例如,在一些实施方案中,本发明方法包括:a)施用本公开的免疫调节组合物;及b)施用一种或多种细胞因子。CC和一种或多种细胞因子可在同一制剂中或在单独的制剂中。CC和一种或多种细胞因子可同时或在不同的时间施用。合适的细胞因子包括但不限于白介素、

转化生长因子(TGF)、成纤维细胞生长因子(FGF)、血小板衍生生长因子(PDGF)、表皮生长因子(EGF)、集落刺激因子(CSF)、结缔组织活化肽(CTAP)、成骨因子、以及所述生长因子的生物活性类似物、片段及衍生物。合适的细胞因子包括B/T细胞分化因子、B/T细胞生长因子、促有丝分裂细胞因子、趋化性细胞因子、集落刺激因子、血管生成因子、IFN-α、IFN-β、IFN-γ、IL1、IL2、IL3、IL4、IL5、IL6、IL7、IL8、IL9、IL10、IL11、IL12、IL13、IL14、IL15、IL16、IL17、IL18、IL22等、瘦素、肌生长抑制素、巨噬细胞刺激蛋白、血小板衍生生长因子、肿瘤坏死因子(TNF)-α(TNF-α)、TNF-β、神经生长因子(NGF)、CD40L、CD137L/4-1BBL、人淋巴毒素-β、G-CSF、M-CSF、GM-CSF、血小板衍生生长因子(PDGF)、IL-1α、IL1-β、IP-10、PF4、GRO、9E3、促红细胞生成素、内皮抑素、制管张素、血管内皮生长因子(VEGF)或其任何片段或组合。其它细胞因子包括转化生长因子(TGF)超基因家族的成员,包括β转化生长因子(例如TGF-β1、TGF-β2、TGF-β3);骨形态发生蛋白(例如BMP-1、BMP-2、BMP-3、BMP-4、BMP-5、BMP-6、BMP-7、BMP-8、BMP-9);肝素结合生长因子(例如成纤维细胞生长因子(FGF)、表皮生长因子(EGF)、血小板衍生生长因子(PDGF)、胰岛素样生长因子(IGF));造血生长因子(Flt3);垂体生长激素或衍生物;生长激素、刺激神经激素、抑制素(例如抑制素A、抑制素B);分化因子(例如GDF-1);以及活化素(例如,活化素A、活化素B、活化素AB)。

[0207] 本发明的组合疗法可包括:施用本公开的免疫调节组合物和一种或多种治疗剂,如抗血管生成剂(例如,在用于治疗实体肿瘤和用于治疗并预防转移的方法中)和抗激素剂(特别是在治疗激素依赖性癌症如乳腺癌和前列腺癌的方法中)。

[0208] 在一个实施方案中,本公开的免疫调节组合物是与一种或多种抗血管生成剂组合施用。这种试剂包括但不限于制管张素、沙利度胺、kringle 5、内皮抑素、Serpin(丝氨酸蛋白酶抑制剂)抗凝血酶、纤连蛋白的29kDa N末端和40kDa C末端蛋白水解片段、催乳素的16kDa蛋白水解片段、血小板因子-4的7.8kDa蛋白水解片段、对应于血小板因子-4的片段的13-氨基酸肽(Maione等人,1990,Cancer Res.51:2077-2083)、对应于胶原I的片段的14-氨基酸肽(Tolma等人,1993,J.Cell Biol.122:497-511)、对应于血小板反应蛋白I的片段的19氨基酸肽(Tolsma等人,1993,J.Cell Biol.122:497-511)、对应于SPARC的片段的20-氨基酸肽(Sage等人,1995,J.Cell.Biochem.57:1329-1334)、或其任何片段、家族成员或变体,包括其药学上可接受的盐。

[0209] 抑制血管生成并且对应于层粘连蛋白、纤连蛋白、前胶原及EGF的其它肽也已有所描述(参见,例如Cao,1998,Prog Mol Subcell Biol.20:161-176)。阻断结合RGD蛋白(即,具有肽基序Arg-Gly-Asp)的某些整联蛋白的单克隆抗体和环状五肽已证明具有抗血管形成活性(Brooks等人,1994,Science 264:569-571;Hammes等人,1996,Nature Medicine 2:529-533)。此外,通过受体拮抗剂抑制尿激酶型纤溶酶原激活物受体将抑制血管生成、肿瘤生长和转移(Min等人,1996,Cancer Res.56:2428-33;Crowley等人,1993,Proc Natl Acad Sci.90:5021-25)。

[0210] 在另一实施方案中,本公开的组合疗法包括施用本公开的免疫调节组合物以及激素治疗模式。这种治疗模式包括施用激素拮抗剂(例如,氟他胺、比卡鲁胺、他莫昔芬、雷洛昔芬、乙酸亮丙瑞林(LUPRON)、LH-RH拮抗剂)、激素生物合成和加工的抑制剂、和类固醇(例如,地塞米松、类视黄醇、deltoids、倍他米松、皮质醇、可的松、强的松、去氢睾酮、糖皮质激素、盐皮质激素、雌激素、睾丸激素、孕酮)、维生素A衍生物(例如,所有反式视黄酸(ATRA));

维生素D3类似物;抗雌激素(例如,米非司酮、奥那司酮)以及抗雄激素(例如,醋酸赛普罗特博)。

[0211] 在另一实施方案中,本公开的免疫调节组合物与利用如反义多核苷酸、核糖酶、RNA干扰分子、三股螺旋多核苷酸等多核苷酸化合物的治疗模式结合使用。

[0212] 在某些实施方案中,本公开的免疫调节组合物与免疫调控剂组合施用。在一些实施方案中,将免疫调节组合物与免疫调控剂一起配制。"免疫调控剂"为抑制、掩蔽或增强所施用的受试者的免疫系统的物质。示例性试剂为抑制细胞因子产生、下调或抑制自身抗原表达、或掩蔽MHC抗原的那些物质。这种试剂的实例包括2-氨基-6-芳基-5-取代的嘧啶(参见,美国专利号4,665,077)、咪唑硫嘌呤(或环磷酰胺,如果存在对咪唑硫嘌呤的不良反应的话);溴隐亭;戊二醛(其掩蔽MHC抗原,如美国专利号4,120,649中所述);针对MHC抗原及MHC片段的抗独特型抗体;环孢菌素A;类固醇,如糖皮质类固醇,例如,强的松、甲基强的松龙及地塞米松;细胞因子或细胞因子受体拮抗剂,包括抗干扰素-γ、-β或α抗体;抗肿瘤坏死因子-a抗体;抗肿瘤坏死因子-β抗体;抗白介素-2抗体及抗IL-2受体抗体;抗-L3T4抗体;异源抗淋巴细胞球蛋白;泛-T抗体,优选抗CD3或抗CD4/CD4a抗体;含有LFA-3结合域的可溶性肽;IDO抑制剂;链激酶;TGF-β;链道酶;FK506;RS-61443;脱氧精胍菌素;以及雷帕霉素。细胞因子的实例包括但不限于淋巴因子、单核因子及传统的多肽激素。包括在细胞因子中的是生长激素,如人生长激素、N-甲硫氨酰基人生长激素及牛生长激素;甲状旁腺激素;甲状腺素;胰岛素;胰岛素原;松弛素;松弛素原;糖蛋白激素,如促卵泡激素(FSH)、胰高血糖素、促甲状腺激素(TSH)及黄体生成素(LH);肝生长因子;成纤维细胞生长因子;催乳素;胎盘催乳素;肿瘤坏死因子-α;苗勒氏抑制物质;小鼠促性腺激素相关肽;抑制素;活化素;血管内皮生长因子;整联蛋白;促血小板生成素(TPO);神经生长因子,如NGF-α;血小板生长因子;转化生长因子(TGF),如TGF-α和TGF-β;胰岛素样生长因子-I和-II;促红细胞生成素(EPO);骨诱导因子;干扰素;集落刺激因子(CSF),如巨噬细胞-CSF(M-CSF);粒细胞-巨噬细胞-CgP(GM-CSP);和粒细胞-CSF(G-CSF);白介素(IL),如IL-1、IL-1a、IL-2、1L-3、IL-4、IL-5、IL-6、IL-7、IL-8、IL-9、IL-11、IL-12、IL-15;肿瘤坏死因子,如TNF-α或TNF-β;及其它多肽因子,包括LIF和kit配体(KL)。如本文所用,术语细胞因子包括来自天然来源或重组细胞培养物的蛋白质及天然序列细胞因子的生物活性等效物。免疫调控剂的其它实例包括美沙拉嗪、美沙拉明、柳氮磺胺吡啶、柳氮磺胺吡啶衍生物、抗组胺药、糖皮质激素、肾上腺素、茶碱、色甘酸钠、抗白细胞三烯、用于鼻炎的抗胆碱能药物、抗胆碱能减充血剂、肥大细胞稳定剂、单克隆抗IgE抗体。

[0213] 在某些实施方案中,本公开的免疫调节组合物是以与一种或多种免疫调节剂(例如细胞因子)的组合疗法形式施用。合适的细胞因子包括但不限于白介素-1(IL-1)、IL-2、IL-3、IL-12、IL-15、IL-18、G-CSF、GM-CSF、促血小板生成素及γ干扰素。

[0214] 调节抗细菌免疫应答的方法

[0215] 本公开提供调节针对细菌或由细菌产生的物质的免疫应答的方法,所述方法包括向有此需要的个体施用有效量的本公开的免疫调节组合物。

[0216] 在一些情况下,与个体中的致病细菌的治疗前数量相比,调节针对细菌或由细菌产生的物质的免疫应答的本公开方法有效地将个体中的细菌数量减少了至少约25%、至少约50%、至少约75%或至少约99%,或者以致于在个体中(例如,在从个体处获得的生物样

品中)不能检测到致病细菌。

[0217] 在一些情况下,调节针对细菌或由细菌产生的物质(如内毒素、毒素、LPS等)的免疫应答的本公开方法有效调控针对致病细菌的免疫应答。致病细菌包括例如革兰氏阳性细菌、革兰氏阴性细菌、分枝杆菌等。致病细菌的非限制性实例包括分枝杆菌属、链球菌属、葡萄球菌属、假单胞菌属、沙门氏菌属、奈瑟氏菌属及李斯特氏菌属。在一些情况下,所述细菌为淋病奈瑟氏菌(Neisseria gonorrhea)、结核分枝杆菌(M.tuberculosis)、麻风分枝杆菌(M.leprae)、单核细胞增多性李斯特氏菌、肺炎链球菌(Streptococcus pneumoniae)、酿脓链球菌(S.pyogenes)、无乳链球菌(S.agalactiae)、绿色链球菌(S.viridans)、粪链球菌(S.faecalis)、金黄色葡萄球菌(S.aureus)、表皮葡萄球菌(S.epidermis)或牛葡萄球菌(S.bovis)。

[0218] 所考虑致病细菌的其它实例包括但不限于革兰氏阳性细菌(例如李斯特氏菌属、杆菌属如炭疽杆菌(Bacillus anthracis)、丹毒丝菌属物种(Erysipelothrix species))、革兰氏阴性细菌(例如,巴尔通氏体属(Bartonella)、布鲁氏杆菌属(Brucella)、伯克霍尔德菌属(Burkholderia)、弯曲杆菌属(Campylobacter)、肠杆菌属(Enterobacter)、埃希氏菌属、弗朗西斯氏菌属(Francisella)、嗜血杆菌(Hemophilus)、克雷伯氏菌属、摩根氏菌属(Morganella)、变形杆菌属(Proteus)、普罗维登斯菌属(Providencia)、假单胞菌属(Pseudomonas)、沙门氏菌属、沙雷氏菌属(Serratia)、志贺氏菌属、弧菌属(Vibrio)及耶尔森氏菌属(Yersinia)物种)、螺旋体细菌(例如,疏螺旋体属(Borrelia)物种,包括引起莱姆病的伯氏疏螺旋体(Borrelia burgdorferi))、厌氧细菌(例如,放线菌属及梭菌属物种)、革兰氏阳性及阴性球菌、肠球菌属物种、链球菌属物种、肺炎球菌属物种、葡萄球菌属物种、奈瑟氏属菌物种。

[0219] 特定的感染性细菌的另外的非限制性实例包括柠檬酸杆菌属(Citrobacter)、衣原体属某些种(Chlamydia spp.)、幽门螺杆菌(Helicobacter pyloris)、伯氏疏螺旋体(Borelia burgdorferi)、嗜肺军团菌(Legionella pneumophila)、鸟分枝杆菌(Mycobacteria avium)、胞内分枝杆菌(M.intracellulare)、堪萨斯分枝杆菌(M.kansaii)、戈氏分枝杆菌(M.gordonae)、非洲分枝杆菌(M.africanum)、金黄色葡萄球菌(Staphylococcus aureus)、脑膜炎奈瑟氏菌(Neisseria meningitidis)、流感嗜血杆菌(Haemophilus influenzae)、炭疽杆菌(Bacillus anthracis)、鼠疫耶尔森菌(Yersinia pestis)、白喉棒杆菌(Corynebacterium diphtheriae)、红斑丹毒丝菌(Erysipelothrix rhusiopathiae)、产气荚膜梭菌(Clostridium perfringens)、破伤风杆菌(Clostridium tetani)、产气肠杆菌(Enterobacter aerogenes)、肺炎克雷伯氏菌(Klebsiella pneumoniae)、多杀性巴氏杆菌(Pasturella multocida)、具核梭杆菌(Fusobacterium nucleatum)、念珠状链杆菌(Streptobacillus moniliformis)、苍白密螺旋体(Treponema pallidium)、细弱密螺旋体(Treponema pertenue)、钩端螺旋体属(Leptospira)、立克次氏体属(Rickettsia)、牙龈卟啉单胞菌(Porphyromonas gingivalis)及衣氏放线菌(Actinomyces israelli)。

[0220] 致病细菌可为野生型、活的、灭活的、热杀的、突变的、减毒的和/或遗传修饰的。

[0221] 在一些情况下,调节针对细菌或由细菌产生的物质的免疫应答的本公开方法包括向有此需要的个体施用免疫调节组合物,且还包括向所述个体施用有效量的抗细菌剂或抗

分枝杆菌剂。抗细菌剂和抗分枝杆菌剂在本领域中是已知的，且包括例如β-内酰胺抗生素、四环素、链霉素、氯霉素、新霉素、短杆菌肽、杆菌肽、磺酰胺、呋喃西林、萘啶酮酸、利福平、氟喹诺酮、异烟肼、吡嗪酰胺、万古霉素、甲氧西林等。

[0222] 合适的抗细菌剂包括例如氨基糖苷类，如氨丁卡霉素、阿泊拉霉素、阿贝卡星、班贝霉素、丁酰苷菌素、达下霉素、双氢链霉素、健霉素、庆大霉素、异帕米星、卡那霉素、小诺米星、新霉素、十一烯酸新霉素、奈替米星、巴龙霉素、核糖霉素、紫苏霉素、壮观霉素、链霉素、烟肼链霉素及托普霉素；祥霉素，如利福酰胺、利福平、利福霉素及利福昔明；β-内酰胺、如碳青霉烯类，如亚胺培南；头孢菌素，如头孢克洛、头孢羟氨下、头孢羟唑、头孢三嗪、孢西酮、头孢唑啉、头孢克肟、头孢甲肟、头孢地嗪、头孢尼西、头孢哌酮、头孢雷特、头孢噻肟、头孢替安、头孢咪唑、头孢匹胺、头孢泊肟酯、头孢沙定、头孢磺啶、头孢他啶、头孢特仑、头孢替唑、头孢布烯、头孢唑肟、头孢曲松、头孢呋辛、头孢唑南、头孢赛曲钠、头孢氨苄、头孢甘酸、头孢利定、头孢菌素、头孢金素、头孢匹林钠、头孢拉定及特头孢氨苄(Pivcefalexin)；头霉素类，如头孢拉宗、头孢美唑、头孢米诺、Cefetan及头孢噻吩；单环类，如氨曲南、卡芦莫南及替吉莫南；氧头孢烯类，如氟氧头孢和Moxolactam；青霉素，如美西林、氮卓脉青霉素匹酯、羟氨苄青霉素、氨苄西林、阿帕西林、阿扑西林、阿唑西林、阿洛西林、巴氨西林、苄基青霉酸、青霉素钠、羧苄青霉素、羧苄青霉素苯酯钠、卡茚西林、氯甲西林、氯唑西林、环己西林、双氯西林、联苯青霉素钠、依匹西林、芬贝西林、Floxicillin、海他西林、仑氨西林、美坦西林、甲氧西林钠、美洛西林、奈夫西林钠、苯唑西林、培那西林、喷沙西林氢碘化物、苄胺青霉素G、苄星青霉素G、二苯甲胺青霉素G、青霉素G钙、海巴明青霉素G、青霉素G钾、普鲁卡因青霉素G、盘尼西林N、青霉素O、青霉素V、苄星青霉素V、海巴明青霉素V、青哌环素、苯氧乙基青霉素钾、哌拉西林、匹凡西林、苯丙西林、喹那西林、磺苄西林、酞氨西林、替莫西林及替卡西林；林可酰胺类，如氯林肯霉素和林肯霉素；大环内酯，如阿奇霉素、碳霉素、克拉霉素、红霉素、醋硬脂红霉素、依托红霉素、葡庚糖酸红霉素、乳糖酸红霉素、丙酸红霉素、硬脂酸红霉素、交沙霉素、柱晶白霉素、麦迪霉素、美欧卡霉素、竹桃霉素、伯霉素、罗他霉素、蔷薇霉素、罗红霉素、螺旋霉素及醋竹桃霉素；多肽，如双霉素、杆菌肽、缬霉素、粘菌素、持久杀菌素、结核放线菌素、镰孢真菌素、短杆菌肽、短杆菌肽S、蜜柑霉素、多粘菌素、多粘菌素B-甲磺酸、原始霉素、瑞斯托菌素、替考拉宁、硫链丝菌肽、结核放线菌素、短杆菌酪肽、短杆菌素、万古霉素、紫霉素、泛酸紫霉素、维及霉素和杆菌肽锌；四环素，如阿哌环素、氯四环素、羟甲金霉素、地美环素、强力霉素、胍甲环素、赖氨甲四环素、甲氯环素、甲烯土霉素、米诺环素、土霉素、青哌环素、匹哌环素、罗利环素、脱甲脱氧四环素、琥氯霉素吡甲四环素及四环素；环丝氨酸；莫匹罗星；及抗结核菌素。合适的抗细菌剂包括对细菌有特异性的抗体。

[0223] 调节抗病毒免疫应答的方法

[0224] 本公开提供调节针对病毒的免疫应答的方法，所述方法包括向有此需要的个体施用有效量的本公开的免疫调节组合物。

[0225] 在一些情况下，调节针对病毒的免疫应答的本公开方法有效地将个体中的病毒(例如，致病病毒)数量减少了至少约25％、至少约50％、至少约75％或至少约99％，或者以致于在个体中(例如，在从个体处获得的生物样品中)不能检测到致病病毒。

[0226] 例如，在一些情况下，调节针对病毒的免疫应答的本公开方法有效地将个体中的病毒载量减少了至少约25％、至少约50％、至少约75％或至少约99％，以致于在个体中(例

如,在从个体处获得的生物样品中)不能检测到致病病毒。在一些情况下,与个体中病毒的基因组拷贝的治疗前数量相比,调节针对病毒的免疫应答的本公开方法有效地将个体中病毒的基因组拷贝数量减少了至少约25%、至少约50%、至少约75%或至少约99%,或者以致于在个体中(例如,在从个体处获得的生物样品中)不能检测到病毒的基因组拷贝。

[0227] 在一些情况下,调控针对病毒的免疫应答的本公开方法调控针对致病病毒的免疫应答。致病病毒包括但不限于疱疹病毒(HSV-1、HSV-2、VZV、EBV、CMV、HHV-6、HHV-8)、流感病毒(Flu A、B)、肝炎病毒(HepA、HepB、HepC、HepD、HepE)、人免疫缺陷病毒(HIV-1、HIV-2)、呼吸道合胞病毒、麻疹病毒、鼻病毒、腺病毒、SARS病毒、乳头状瘤病毒、正痘病毒、西尼罗病毒(West Nile viruses)及登革热病毒。致病病毒包括黄病毒科病毒的成员。致病病毒包括选自由以下组成的组的黄病毒:登革热病毒、库宁(Kunjin)病毒、日本脑炎(Japanese encephalitits)病毒、西尼罗病毒及黄热病病毒。致病病毒包括淋巴细胞性脉络丛脑膜炎病毒、乙型肝炎病毒、爱泼斯坦巴尔病毒(Epstein Barr virus)及人免疫缺陷病毒。致病病毒包括但不限于逆转录病毒科(Retroviridae)(例如人免疫缺陷病毒,如HIV-1,也称为LAV或HTLV-III/LAV,或HIV-III;及其它分离株,如HIV-LP;小核糖核酸病毒科(Picornaviridae)(例如脊髓灰质炎病毒、甲型肝炎病毒;肠道病毒、人柯萨奇病毒(human Coxsackie viruses)、鼻病毒、埃可病毒);杯状病毒科(Calciviridae)(例如,引起肠胃炎的毒株);披膜病毒科(Togaviridae)(例如马脑炎病毒、风疹病毒);黄病毒科(Flaviridae)(例如登革热病毒、脑炎病毒、黄热病病毒);冠状病毒科(Coronaviridae)(例如冠状病毒);弹状病毒科(Rhabdoviridae)(例如水疱性口腔炎病毒、狂犬病病毒);丝状病毒科(Filoviridae)(例如埃博拉样病毒(ebola-like viruses);马伯格氏病毒(Marburg virus));副粘病毒科(Paramyxoviridae)(例如副流感病毒、腮腺炎病毒、麻疹病毒、呼吸道合胞病毒);正粘病毒科(Orthomyxoviridae)(例如流感病毒);布尼亚病毒科(Bungaviridae)(例如汉坦病毒(Hantaan viruses)、布尼亚(bunga)病毒、白蛉热病毒及内罗(Nairo)病毒);砂粒病毒科(Arenaviridae)(出血热病毒);呼肠孤病毒科(Reoviridae)(例如呼肠孤病毒、环状病毒及轮状病毒);波尔纳病病毒科(Bornaviridae);嗜肝DNA病毒科(Hepadnaviridae)(乙型肝炎病毒);细小病毒科(Parvoviridae)(细小病毒);乳多空病毒科(Papovaviridae)(乳头状瘤病毒、多形瘤病毒);腺病毒科(Adenoviridae)(例如腺病毒);疱疹病毒科(Herpesviridae)(单纯疱疹病毒(HSV)1和2)、水痘带状疱疹病毒、巨细胞病毒(CMV)、疱疹病毒;痘病毒科(Poxviridae)(天花病毒、牛痘病毒、痘病毒);及虹彩病毒科(Iridoviridae)(例如非洲猪瘟病毒(African swine fever virus));以及未分类的病毒(例如海绵状脑病的病原体、丁型肝炎的病原体,被视为乙型肝炎病毒的有缺陷的卫星)、非甲非乙型肝炎的病原体(1类,内部传播;2类,胃肠外传播,即丙型肝炎病毒);诺沃克和相关病毒(Norwalk and related viruses)及星状病毒。

[0228] 在一些情况下,调节针对病毒的免疫应答的本公开方法包括向有此需要的个体施用免疫调节组合物,且还包括向所述个体施用有效量的至少一种另外的治疗剂,例如抗病毒剂。

[0229] 抗病毒剂在本领域中是已知的并且包括例如抗HCV剂,如病毒唑及其类似物;糖苷酶抑制剂;葡糖苷酶抑制剂;IRES(内部核糖体进入位点)、p7、进入、融合、解旋酶、组装、外出、NS2、NS3、NS4、NS5a及NS5B抑制剂;肌苷一磷酸脱氢酶抑制剂;亲环蛋白抑制剂;金属蛋

白酶抑制剂;抗HCV核苷(酸)及非核苷RNA聚合酶抑制剂等;抗HIV剂;抗HBV剂;等等。

[0230] 在一些实施方案中,所述至少一种另外的治疗剂为干扰素(例如,干扰素-α、干扰素-β、干扰素-γ、干扰素-λ、干扰素-τ、干扰素-ω等)。在一些实施方案中,所述至少一种另外的治疗剂为IFN-α。在一些实施方案中,所述至少一种另外的治疗剂为IFN-β。

[0231] 用于治疗HCV感染的合适的另外的抗病毒剂包括但不限于病毒唑及其前药,如盐酸塔利韦林、特拉匹韦、索菲布韦、波普瑞韦、西鲁瑞韦、西咪匹韦、丹诺普韦、范尼普韦、MK-5172、MK-0608、2'-C-甲基-7-去氮腺苷、2'-C-甲基-腺苷、BI201335、那拉普韦(narlaprevir)、阿那匹韦、GS-9256、GS-9451、ABT-450、IDX-320、ACH-1625、瓦洛他滨、mericitabine、R1626、PSI-938、INX-189、BILN1941、BI-207127、VCH222、VX-135、ANA598、ANA773、ABT-072、ABT-333、HCV-796、GS-9190、Daclatasavir、BMS-824393、BMS-791325、PPI-461、GS-5885、阿拉泊韦(Debio-025)、NIM-811、SCY-635、硝唑尼特、克立咪唑、miravirasen、西戈斯韦、BCX-5191、GSK-2336805、抗-PD-1抗体(CT-011)、巴维昔单抗(抗磷脂酰丝氨酸Mab)、治疗性疫苗(GI-5005、IC-41、TG-4040)预防性疫苗(如HCV E1/E2/MF-59)及其前药。合适的另外的治疗剂包括例如用于治疗乙型肝炎病毒感染的治疗剂,包括但不限于拉米夫定、阿德福韦、恩替卡韦、telbuvudine、替诺福韦及其前药。

[0232] 例如,用于治疗HCV感染的合适的另外的抗病毒剂包括聚乙二醇化IFN-α的每周注射与病毒唑(1-β-D-呋喃核糖基-1H-1,2,4-三唑-3-甲酰胺)的每天两次口服剂量的组合。

[0233] 合适的另外的治疗剂包括例如用于治疗免疫缺陷病毒感染或用于治疗可伴随免疫缺陷病毒感染的病症(例如细菌感染、真菌感染等)的治疗剂。合适的另外的治疗剂包括例如β-内酰胺抗生素、四环素、氯霉素、新霉素、短杆菌肽、杆菌肽、磺酰胺、呋喃西林、萘啶酮酸、可的松、氢化可的松、倍他米松、地塞米松、氟考龙、泼尼松龙、曲安奈德、吲哚美辛、舒林酸、阿昔洛韦、金刚烷胺、金刚烷乙胺、重组可溶性CD4(rsCD4)、蓝藻抗病毒蛋白-N、microvirin、恩夫韦、抗受体抗体(例如针对鼻病毒)、奈韦拉平、西多福韦(Vistide™)、磷甲酸三钠(Foscarnet™)、泛昔洛韦、喷昔洛韦、伐昔洛韦、核酸/复制抑制剂、干扰素、叠氮胸苷(AZT,Retrovir™)、去羟肌苷(双去氧肌苷,ddI,Videx™)、司他夫定(d4T,Zerit™)、扎西他宾(双脱氧胞苷,ddC,Hivid™)、奈韦拉平(Viramune™)、拉米夫定(Epivir™,3TC)、蛋白酶抑制剂、沙奎那韦(Invirase™、Fortovase™)、利托那韦(Norvir™)、奈非那韦(Viracept™)、依法韦仑(Sustiva™)、阿巴卡韦(Ziagen™)、安普那韦(Agenerase™)茚地那韦(Crixivan™)、更昔洛韦、AzDU、地拉韦啶(Rescriptor™)、洛匹那韦(kaletra)、三协维、利福平、clathiromycin、促红细胞生成素、集落刺激因子(G-CSF和GM-CSF)、非核苷逆转录酶抑制剂、核苷抑制剂、病毒进入抑制剂、融合抑制剂、整合酶抑制剂、阿霉素、氟尿嘧啶、氨甲蝶呤、天冬酰胺酶及其组合。用于HIV的另外的合适的治疗剂包括整合酶和融合抑制剂,如雷特格韦、艾特格韦、恩夫韦地、马拉维若等。

[0234] 在一些实施方案中,至少一种另外的治疗剂为神经氨糖酸苷酶抑制剂,例如,其中流感病毒为流感A或流感B。合适的神经氨糖酸苷酶抑制剂包括例如奥司他韦((3R,4R,5S)-5-氨基-4-乙酰胺基-3-(戊烷-3-基氧基)环己-1-烯-1-甲酸乙酯;Tamiflu™)、扎那米韦(2R,3R,4S)-4-[(二氨基亚甲基)氨基]-3-乙酰胺基-2-[(1R,2R)-1,2,3-三羟基丙基]-3,4-二氢-2H-吡喃-6-甲酸;Relenza™)、及帕拉米韦(1S,2S,3S,4R)-3-[(1S)-1-乙酰胺基-2-乙基-丁基]-4-(二氨基亚甲基氨基)-2-羟基-环戊烷-1-甲酸)。在一些实施方案中,至少一

种另外的治疗剂为M2阻断剂，例如阻断病毒性离子通道(M2蛋白)。抗病毒药物金刚烷胺和金刚烷乙胺为M2阻断剂，并且可用于本方法中。

[0235] 例如用于治疗HSV-1或HSV-2感染的合适的另外的治疗剂包括但不限于阿昔洛韦(Zovirax)、缬更昔洛韦、泛昔洛韦、伐昔洛韦(Valtrex)、更昔洛韦(Cytovene)、西多福韦(Vistide)、反义寡核苷酸福米韦生(Vitravene)、膦甲酸(Foscavir)、喷昔洛韦、碘苷、阿糖腺苷及曲氟尿苷。

[0236] 在一些实施方案中，所述一种或多种不同治疗剂为所选出的靶向两种或更多种不同病毒的抗病毒剂；例如，HIV抑制剂、HBV抑制剂、HCV抑制剂、疱疹病毒抑制剂、流感病毒抑制剂、RNA抑制剂、干扰RNA(RNAi)抑制剂、天然产物等。在一些情况下，治疗病毒感染的本公开方法包括向有此需要的个体施用免疫调节组合物，且还包括向所述个体施用有效量的至少一种另外的治疗剂，例如，单克隆抗体或针对病毒抗原的抗体产物，其中合适的单克隆抗体包括但不限于HBIg、针对流感病毒毒株的抗体、抗甲型肝炎病毒抗体、SYNAGIS(抗RSV Mab)、抗狂犬病抗体、ostavir(抗HBV Mab)、Pro542(抗HIV gp120)、Potovir(抗CMV Mab)、抗PD-1抗体(CT-011)、巴维昔单抗(抗磷脂酰丝氨酸Mab)等。

[0237] 调节针对寄生虫感染的免疫应答的方法

[0238] 本公开提供调节针对微生物寄生虫(例如，致病原生动物；蠕虫；等)的免疫应答的方法，所述方法包括向有此需要的个体施用有效量的本公开的免疫调节组合物。

[0239] 在一些情况下，与个体中的微生物寄生虫的治疗前数量相比，调节针对微生物寄生虫的免疫应答的本公开方法有效地将个体中的微生物寄生虫(例如，致病原生动物；致病蠕虫)数量减少了至少约25％、至少约50％、至少约75％或至少约99％，或者以致于在个体中(例如，在从个体处获得的生物样品中)不能检测到微生物寄生虫。

[0240] 在一些情况下，调节针对微生物寄生虫的免疫应答的本公开方法包括向有此需要的个体施用免疫调节组合物，且还包括向所述个体施用有效量的至少一种另外的治疗剂。抗寄生虫剂在本领域中是已知的并且包括例如氯喹等。例如，抗疟疾剂包括例如奎宁、氯喹、阿托伐醌、氯胍、伯氨喹、氨酚喹、甲氟喹、喹哌、青蒿素、次甲基蓝、乙胺嘧啶、磺胺多辛、蒿甲醚-苯芴醇、氨苯砜-氯丙胍、青蒿琥酯、奎尼丁、氯羟吡啶、吡啶/吡啶酚类似物、4(1H)-喹啉酮类似物、双氢青蒿素、阿托伐醌与氯胍的混合物、内过氧化物及吖啶酮。抗寄生虫剂包括对寄生虫有特异性的抗体。

[0241] 在一些情况下，调节(例如降低)针对微生物寄生虫的免疫应答的本公开方法调节针对以下微生物寄生虫的免疫应答：如疟原虫属某些种(Plasmodium spp.)、刚地弓形虫(Toxoplasma gondii)、巴贝西虫属某些种(Babesia spp.)、旋毛线虫(Trichinella spiralis)、痢疾内变形虫(Entamoeba histolytica)、蓝氏贾第鞭毛虫(Giardia lamblia)、比氏肠胞虫(Enterocytozoon bieneusi)、纳氏虫属(Naegleria)、棘阿米巴属(Acanthamoeba)、罗德西亚锥虫(Trypanosoma rhodesiense)和冈比亚锥虫(Trypanosoma gambiense)、等孢子球虫属某些种(Isospora spp.)、隐孢子虫属某些种(Cryptosporidium spp.)、艾美虫属某些种(Eimeria spp.)、新孢子虫属某些种(Neospora spp.)、肉孢子虫属某些种(Sarcocystis spp.)及血吸虫属某些种(Schistosoma spp)。

[0242] 在一些情况下，调节(例如降低)针对原生动物寄生虫的免疫应答的本公开方法调节针对以下原生动物寄生虫的免疫应答：如贾第鞭毛虫属；疟原虫属物种(例如镰状疟原虫

(Plasmodium falciparum));刚地弓形虫;隐孢子虫属;毛滴虫属(Trichomonas)物种;锥虫(例如克氏锥虫(Trypanosoma cruzi));或利什曼虫属(Leishmania)。

[0243] 调节针对致病真菌的免疫应答的方法

[0244] 本公开提供调节对致病真菌的免疫应答的方法,所述方法包括向有此需要的个体施用有效量的本公开的免疫调节组合物。

[0245] 在一些情况下,与个体中的真菌体的治疗前数量相比,调节针对致病真菌的免疫应答的本公开方法有效地将个体中的真菌体数量减少了至少约25%、至少约50%、至少约75%或至少约99%,或者以致于在个体中(例如,在从个体处获得的生物样品中)不能检测到致病真菌。

[0246] 在一些情况下,调节(例如降低)针对致病真菌的免疫应答的本公开方法诱导或调节针对以下真菌的免疫应答:如念珠菌属某些种(Candida spp.),包括白色念珠菌(C.albicans);曲霉属某些种(Aspergillus spp.);隐球酵母属(Cryptococcus spp.),包括新型隐球菌(C.neoformans);芽生菌属某种(Blastomyces sp.);肺细胞属某些种(Pneumocytes spp.)或球孢子菌属某些种(Coccidioides spp.)。

[0247] 在一些情况下,调节针对致病真菌的免疫应答的本公开方法包括向有此需要的个体施用免疫调节组合物,且还包括向所述个体施用有效量的至少一种另外的治疗剂。抗真菌剂在本领域中是已知的并且包括例如氟康唑、5-氟胞嘧啶等。

[0248] 合适的抗真菌剂包括例如多烯类,如两性霉素-B(包括两性霉素-B的各种制剂)、杀假丝菌素、制皮菌素、菲律宾菌素、制霉色基素、八丈岛霉素、哈霉素、鲁斯霉素、美帕曲星、游霉素、制霉菌素、拟青霉素及表霉素;及其它,如重氮丝氨酸、灰黄霉素、寡霉素、十一碳烯酸新霉素、吡咯尼群、干蠕孢菌素、杀结核菌素及绿胶霉素;烯丙胺类,如萘替芬和特比萘芬;咪唑类,如联苯苄唑、布康唑、氯登妥因、氯苄达唑、氯康唑、克霉唑、益康唑、恩康唑、芬替康唑、异康唑、酮康唑、霉康唑、奥莫康唑、奥昔康唑、硝酸盐、硫康唑及噻康唑;三唑类,如氟康唑、伊曲康唑及特康唑;及其它,如吖啶琐辛、阿莫罗芬、苯柳胺酯、溴柳氯苯胺、丁氯柳胺、丙酸钙、Chlophenesin、环匹罗司、氯羟喹啉、Coparaffinate、双胺噻唑、二盐酸盐、依沙酰胺、氟胞嘧啶、哈利他唑、海克替啶、氟苯氯苯硫脲、硝呋太尔、碘化钾、丙酸、羟基吡啶硫酮、水杨酰苯胺、丙酸钠、二苯嗪硫酮、替诺尼唑、托西拉酯、托林达酯、托萘酯、五羟黄酮、苄硫噻二嗪乙酸、十一碳烯酸及丙酸锌。

[0249] 治疗过敏性疾病的方法

[0250] 本公开提供治疗个体中的过敏性疾病如哮喘、过敏性鼻炎、结膜炎、特应性皮炎的方法,所述方法包括向所述个体施用有效量的本公开的免疫调节组合物。在一些情况下,本公开的治疗过敏性疾病的方法包括向有此需要的个体施用有效量的本公开的免疫调节组合物,其中所述免疫调节组合物包含过敏原。合适的过敏原如上所述。

[0251] 在一些情况下,治疗过敏性疾病的本公开方法有效调控免疫应答。在一些情况下,与治疗前水平相比,治疗过敏性疾病的本公开方法有效减少以下一个或多个:a)个体中的IgE水平;b)个体中的过敏原特异性IgE的水平;c)个体中的肥大细胞数量;d)个体中的组胺水平;以及e)个体中的IL-4水平。

[0252] 在一些情况下,治疗过敏性疾病的本公开方法包括向有此需要的个体施用免疫调节组合物,且还包括向所述个体施用有效量的至少一种另外的治疗剂。合适的另外的治疗

剂包括例如抗组胺药、类固醇(例如皮质类固醇)、前列腺素诱导物、抗炎剂、白细胞三烯拮抗剂、IL-4突变蛋白、可溶性IL-4受体、免疫抑制剂(如耐受肽疫苗)、抗IL-4抗体、IL-4拮抗剂、抗IL-5抗体、可溶性IL-13受体-Fc融合蛋白、抗IL-9抗体、CCR3拮抗剂、CCR5拮抗剂、VLA-4抑制剂及IgE的下调剂。合适的类固醇包括但不限于倍氯米松、氟替卡松、曲安缩松、布地缩松、皮质类固醇及布地缩松。

[0253] 治疗自身免疫病症的方法

[0254] 本公开提供治疗个体中的自身免疫病症的方法,所述方法包括向所述个体施用有效量的本公开的免疫调节组合物。自身免疫病状引起许多自身免疫病症,如类风湿性关节炎、哮喘、1型糖尿病、多发性硬化症、全身性红斑狼疮(SLE)、斯耶格伦综合征、动脉粥样硬化、自身免疫肝炎、自身免疫胰腺炎、乳糜泻、自身免疫性溶血性贫血、强直性脊柱炎、自身免疫疾病相关癌症、自身免疫疾病相关纤维化等。通过用本公开的免疫调节组合物调节先天性和适应性免疫机制,可治疗自身免疫病症。在一些情况下,治疗自身免疫病症的本公开方法包括向有此需要的个体施用有效量的本公开的免疫调节组合物,其中所述免疫调节组合物包含自身抗原。合适的自身抗原如上所述。

[0255] 在一些情况下,与自身反应性T细胞的治疗前数量和/或活性相比,治疗自身免疫病症的本公开方法有效地将个体中的自身反应性T细胞的数量和/或活性减少了至少约25%、至少约50%、至少约75%或至少约99%,或者以致于在个体中(例如,在从个体处获得的生物样品中)不能检测到自身反应性T细胞。

[0256] 在一些情况下,与自身抗体的治疗前水平相比,治疗自身免疫病症的本公开方法有效地将个体中的自身抗体水平降低了至少约25%、至少约50%、至少约75%或至少约99%,或者以致于在个体中(例如,在从个体处获得的生物样品中)不能检测到自身抗体。

[0257] 在一些情况下,与细胞因子的治疗前水平相比,治疗自身免疫病症的本公开方法有效地将个体中的细胞因子水平调节了至少约25%、至少约50%、至少约75%或至少约99%,或者以致于在个体中(例如,在从个体处获得的生物样品中)不能检测到细胞因子。

[0258] 在一些情况下,治疗自身免疫病症的本公开方法包括向有此需要的个体施用免疫调节组合物,且还包括向所述个体施用有效量的至少一种另外的治疗剂。可用于治疗自身免疫病症的治疗剂的实例包括但不限于抗炎剂;免疫抑制剂(例如皮质类固醇(例如强的松、皮质醇、甲基强的松龙等))、环孢菌素A);细胞毒性剂(例如6-巯基嘌呤、咪唑硫嘌呤、氨甲蝶呤、烷化剂、抗代谢物剂);植物碱;天然产物;甾体激素;低氧剂;抗增殖剂;抗癌剂;达那唑;colchisine;左旋四咪唑;生物应答调节剂等等。

[0259] 也可用于治疗自身免疫病症的治疗剂的实例包括用于减少细胞增殖的试剂,其在本领域中是已知的并且广泛使用。这种试剂包括烷化剂,如氮芥类、亚硝基脲、氮丙啶衍生物、烷基磺酸盐及三氮烯,包括但不限于二氯甲基二乙胺(mechlorethamine)、环磷酰胺(Cytoxan.TM.)、美法仑(L-溶肉瘤素)、卡莫司汀(BCNU)、洛莫司汀(CCNU)、司莫司汀(甲基-CCNU)、链脲霉素、氯脲霉素、尿嘧啶氮芥、双氯乙基甲胺(chlormethine)、异环磷酰胺、氮芥苯丁酸、双溴丙基哌嗪、曲他胺、三亚乙基硫代磷酰胺、白消安、氮烯唑胺及替莫唑胺。

[0260] 抗代谢剂包括叶酸类似物、嘧啶类似物、嘌呤类似物及腺苷脱氨酶抑制剂,包括但不限于阿糖胞苷(CYTOSAR-U)、胞嘧啶阿拉伯糖苷、氟尿嘧啶(5-FU)、氟尿苷(FudR)、6-硫代鸟嘌呤、6-巯基嘌呤(6-MP)、喷司他丁、5-氟尿嘧啶(5-FU)、氨甲蝶呤、10-炔丙基-5,8-二脱

氮杂叶酸盐(PDDF,CB3717)、5,8-二脱氮杂四氢叶酸(DDATHF)、甲酰四氢叶酸、磷酸氟达拉滨、喷司他丁、吉西他滨、环胞苷、胍唑、肌苷乙二醇二醛、EICAR、病毒唑、噻唑扶林、去铁胺(defroxamine)及吡唑并咪唑。

[0261] 合适的天然产物及它们的衍生物(例如长春花生物碱、抗肿瘤抗生素、酶、淋巴因子及表鬼臼毒素)包括但不限于Ara-C、紫杉醇(Taxol®)、多西他赛(Taxotere®)、脱氧柯福霉素、丝裂霉素-C、L-天冬酰胺酶、咪唑硫嘌呤;布喹那;生物碱,例如长春新碱、长春花碱、长春瑞滨、长春地辛等;鬼臼霉素,例如依托泊苷、替尼泊苷、喜树碱等;抗生素,例如蒽环霉素、盐酸柔红霉素(道诺霉素、红比霉素、柔红霉素)、伊达比星、阿霉素、表柔比星及吗啉代衍生物等;phenoxizone双环肽,例如更生霉素;碱性糖肽,例如博来霉素;蒽醌甙,例如普卡霉素(光神霉素);蒽二酮,例如米托蒽醌;氮丙啶吡咯并吲哚二酮,例如丝裂霉素;大环免疫抑制剂,例如环孢菌素、FK-506(他克莫司,普乐可复)、雷帕霉素等;抗血管类黄酮;等等。其它试剂包括矿物质、营养素、维生素、增补剂、抗氧化剂、药草、香料(姜、牛至、丁香等)、天然保健品(绿茶、鱼油等)及抗炎治疗和形式。

[0262] 其它抗增殖细胞毒性剂为诺维本(navelbene)、CPT-11、阿那曲唑、来曲唑、卡培他滨、雷洛昔芬、环磷酰胺、叶酸、视黄酸、异环磷酰胺及多洛克方(droloxafine)。其它合适的抗增殖剂包括siRNA、干扰RNA(RNAi)及反义RNA。

[0263] 具有抗增殖活性的微管影响剂也是适用的且包括但不限于别秋水仙碱(NSC 406042)、软海绵素B(NSC 609395)、秋水仙碱(NSC 757)、秋水仙碱衍生物(例如NSC 33410)、多拉司他汀10(NSC 376128)、美登素(NSC 153858)、利索新(NSC 332598)、紫杉醇(Taxol®)、Taxol®衍生物、多西他赛(Taxotere®)、硫代秋水仙碱(NSC 361792)、三苯甲基半胱氨酸(trityl cysterin)、硫酸长春碱、硫酸长春新碱、天然和合成的埃博霉素,包括但不限于埃博霉素A、埃博霉素B、圆皮海绵内酯;雌氮芥、诺考达唑等。

[0264] 适用的激素调节剂和类固醇(包括合成类似物)包括但不限于肾上腺类固醇,例如强的松、地塞米松等;雌激素和孕酮,例如己酸羟孕酮、醋酸甲羟孕酮、醋酸甲地孕酮、雌二醇、哥罗米酚、他莫昔芬等;及肾上腺皮质抑制剂,例如氨鲁米特;17α-乙炔雌二醇;己烯雌酚、睾丸激素、氟羟甲睾酮、丙酸屈他雄酮、睾内酯、甲基强的松龙、甲基睾丸激素、泼尼松龙、曲安奈德、氯三芳乙烯、羟孕酮、氨鲁米特、雌氮芥、醋酸甲羟孕酮、亮丙瑞林、氟他胺(Drogenil)、托瑞米芬(Fareston)及Zoladex®。雌激素刺激增殖和分化;因此,结合至雌激素受体的化合物用于阻断此活性。皮质类固醇可抑制T细胞增殖。

[0265] 其它细胞毒性剂包括金属配合物,例如顺铂(顺式-DDP)、卡铂等;脲,例如羟基脲;及肼,例如N-甲肼;表鬼臼毒素;拓扑异构酶抑制剂,例如依立替康、磷酸足叶乙甙、米托蒽醌;甲基苄肼;米托蒽醌;甲酰四氢叶酸;替加氟等。所关注的其它抗增殖剂包括免疫抑制剂,例如霉酚酸、沙利度胺、脱氧司加林、azasporine、来氟米特、咪唑立宾、氮杂螺烷(azaspirane)(SKF 105685);Iressa®(ZD 1839,4-(3-氯-4-氟苯基氨基)-7-甲氧基-6-(3-(4-吗啉基)丙氧基)喹唑啉);等等。

[0266] 适于与本公开方法结合使用的生物应答调节剂包括但不限于:(1)酪氨酸激酶(RTK)活性抑制剂;(2)丝氨酸/苏氨酸激酶活性抑制剂;(3)肿瘤相关抗原拮抗剂,如特异性地结合至肿瘤抗原的抗体;(4)细胞凋亡受体激动剂;(5)白介素-2;(6)干扰素-α;(7)干扰

素-γ；(8)集落刺激因子；(9)血管生成抑制剂；(10)肿瘤坏死因子拮抗剂子；及(11)BRAF抑制剂。

[0267] 治疗包括免疫失调的疾病的方法

[0268] 本公开提供调节、恢复和/或调控个体中的免疫功能障碍的方法，所述方法包括向所述个体施用有效量的本公开的免疫调节组合物。免疫功能障碍病状引起许多疾病，如类风湿性关节炎(RA)及相关疾病、糖尿病、牛皮癣、全身性红斑狼疮(SLE)及相关疾病、移植物抗宿主疾病(GVHD)、溃疡性结肠炎、细菌诱导的结肠炎、克罗恩氏病、斑形脱发、哮喘、过敏性鼻炎、结膜炎、移植排斥、桥本氏甲状腺炎、炎性肠病(IBD)、短肠综合征及其它胃肠病症(如克罗恩氏病、溃疡性结肠炎)、心血管疾病、肥胖、伤口愈合、烧伤恢复、衰老、体重增加、脂肪沉积等。肠粘膜表面处的免疫应答失调可通过增加来自肠道的微生物及微生物产物的移位而造成全身性免疫系统激活。通过用本公开的免疫调节组合物调节先天性和适应性免疫机制(包括免疫细胞、细胞因子、抗体等)，免疫失调可得到预防和/或治疗。

[0269] 在一些情况下，治疗免疫功能障碍病症的本公开方法包括向有此需要的个体施用免疫调节组合物，且还包括向所述个体施用有效量的至少一种另外的治疗剂。

[0270] 在一些情况下，所述方法包括向有此需要的个体施用有效量的呈疫苗形式的本公开的免疫调节组合物，所述疫苗包含将调节针对疾病相关抗原的有障碍的免疫应答的抗原。

[0271] 在一些情况下，所述方法包括向有此需要的个体施用有效量的本公开的免疫调节组合物以便保护、调节、恢复或纠正患者微生物组中的疾病或医学病状相关的不平衡。微生物群中的平衡失调引起了各种病症，如皮肤病状、活跃的炎性应答、炎症相关癌症、早产、不育症、女性避孕、泌尿生殖器感染、性传播疾病等。

[0272] 本发明的另一方面包括通过大体上增加或减少受试者的微生物区的相对丰度的治疗方法。

[0273] 在一些情况下，治疗免疫失调并恢复体内平衡的本公开方法包括向有此需要的个体施用免疫调节组合物，且还包括向所述个体施用有效量的所述微生物组的一个或多个成员或益生菌。

[0274] 治疗包括不希望的炎性活性的疾病的方法

[0275] 本公开提供调节和/或调控个体中不希望的炎性活性的方法，所述方法包括向有此需要的个体施用有效量的本公开的免疫调节组合物。不希望的炎性病状造成许多疾病，如腹泻病、由化疗或放疗引起的粘膜炎、由感染因子或抗生素引起的肠胃炎、结肠袋炎、肥胖相关炎症、阑尾炎、器官(肝、肾、肺、心、胰岛等)移植、细菌感染、病毒感染、真菌感染、癌症相关炎症、泌尿生殖器疾病、细菌性阴道病、手术相关损伤、败血症、厌食症、高草酸尿症、溃疡、伤口愈合、肾病、肝病、肝纤维化、酒精性肝炎、纤维化疾病如肺纤维化、肾纤维化、特发性肺纤维化、痤疮、不希望的呼吸道炎性活性、炎症相关癌症、炎症相关器官(肺、肝、肾、心、胃肠道、脑等)损伤和损害、自发炎症疾病(如TNF受体相关周期性综合征、杜宾-强生综合征(Dubin Johnson syndrome)、白塞氏病(Behcet's disease)、家族性地中海热等)等。通过用本公开的免疫调节组合物调节先天性和适应性免疫机制(包括免疫细胞、细胞因子、趋化因子、抗体等)，炎性病症可得到预防和/或治疗。

[0276] 在本发明的一个方面，控制不希望的炎性应答还包括调节激素、前列腺素、反应性

中间体及白细胞三烯的水平。

[0277] 在一些情况下，治疗炎性病症的本公开方法包括向有此需要的个体施用免疫调节组合物，且还包括向所述个体施用有效量的至少一种另外的治疗剂、微生物组的一个或多个成员或益生菌。可用于治疗炎性病状的治疗剂的实例包括但不限于抗炎剂；免疫抑制剂；细胞毒性剂等。

[0278] 可用于治疗炎性病状的治疗剂的其它非限制性实例包括：钙调磷酸酶抑制剂(例如，吡美莫司、他克莫司等)、氨甲蝶呤、环孢菌素和局部试剂(例如，他扎罗汀、蒽林、卡泊三烯(calciprotriene)、皮质类固醇等)。

[0279] 在一些情况下，所述方法包括向有此需要的个体施用有效量的呈疫苗形式的本公开的免疫调节组合物，所述疫苗包含将调节针对疾病相关抗原的炎性免疫应答的抗原。

[0280] 所述组合物适于治疗的自身免疫疾病、免疫失调、炎症、过敏性疾病、真皮疾病、感染性疾病及器官移植的其它实例包括以下疾病，如原发性硬化性胆管炎、口炎性腹泻、自身免疫性关节炎、莱姆关节炎、牛皮癣关节炎、反应性关节炎、脊柱关节病、皮炎、硬皮病、结节病、弥漫性血管内凝血、川崎病(Kawasaki's disease)、肾病综合征、慢性疲劳综合征、纤维肌痛、韦格纳氏肉芽肿病(Wegener's granulomatosis)、亨-舍二氏紫癜(Henoch-Schoenlejn purpurea)、显微镜下肾血管炎、慢性活动性肝炎、葡萄膜炎、败血性休克、中毒性休克综合征、败血症综合征、恶病质、获得性免疫缺陷综合征、急性横贯性脊髓炎、亨廷顿氏舞蹈病(Huntington's chorea)、原发性胆汁性肝硬化、溶血性贫血、I型多腺体缺陷综合征和II型多腺体缺陷综合征、施密特氏综合征(Schmidt's syndrome)、成人(急性)呼吸窘迫综合征、血清反应阴性关节病、关节病、莱特尔氏病(Reiter's disease)、牛皮癣性关节病、衣原体、耶尔森氏菌属和沙门氏菌属相关关节病、脊柱关节病、动脉粥样硬化性疾病/动脉硬化、过敏性结肠炎、特异反应性过敏、食物过敏如花生过敏、树坚果过敏、蛋过敏、牛奶过敏、大豆过敏、小麦过敏、海鲜过敏、贝类过敏或芝麻籽过敏、自身免疫大疱病、寻常天疱疮、落叶型天疱疮、类天疱疮、线性IgA疾病、自身免疫性溶血性贫血、库姆阳性溶血性贫血(Coombs positive haemolytic anaemia)、获得性恶性贫血、幼年型恶性贫血、肌痛性脑炎/贵族自由疾病(Royal Free Disease)、自身免疫性脑脊髓炎、慢性皮肤粘膜念珠菌病、巨细胞性动脉炎、非酒精性脂肪肝疾病、脂肪性肝炎、原发性硬化性肝炎、隐原性自身免疫性肝炎、获得性免疫缺陷相关疾病、丙型肝炎、常见变异型免疫缺陷(常见变异型血丙种球蛋白过少)、扩张型心肌病、纤维化肺病、隐原性纤维性肺泡炎、炎症后间质性肺病、间质性肺炎、结缔组织疾病相关的间质性肺病、混合结缔组织病相关的肺病、全身性硬化相关的间质性肺病、斯耶格伦病(Sjogren's disease)相关的肺病、强直性脊柱炎相关的肺病、血管炎弥漫性肺病、含铁血黄素沉着相关的肺病、药物诱导的间质性肺病、放射后肺纤维化、闭塞性细支气管炎、慢性嗜酸细胞性肺炎、淋巴细胞性渗透性肺病、感染后间质性肺病、痛风性关节炎、1型自身免疫性肝炎(典型的自身免疫性或狼疮样肝炎)、2型自身免疫性肝炎(抗LKM抗体肝炎)、自身免疫介导的低血糖、伴有黑棘皮病的B型胰岛素抗性、甲状旁腺机能减退、骨关节病、原发性硬化性胆管炎、特发性白细胞减少、自身免疫性中性粒细胞减少症、肾病NOS、肾小球性肾炎、显微镜下肾血管炎、盘状狼疮、红斑狼疮、男性不育症、特发性或NOS、精子自身免疫、交感性眼炎、继发于结缔组织疾病的肺高血压、古德帕斯彻氏综合征(Goodpasture's syndrome)、多发性结节性动脉炎的肺部表现、急性风湿热、类风湿性脊椎

炎,斯提耳氏病(Still's disease)、全身性硬化、高安氏病(Takayasu's disease)/动脉炎、自身免疫性血小板减少症、特发性血小板减少症、自身免疫性甲状腺病、甲状腺机能亢进、萎缩性自身免疫性甲状腺机能减退、原发性黏液腺瘤病、晶状体源性葡萄膜炎、原发性血管炎、白斑病、过敏症、宠物过敏、乳液过敏、药物过敏、过敏性鼻结膜炎、嗜曙红的食管炎、嗜酸性白细胞增多综合征、嗜酸细胞性肠胃炎、皮肤红斑狼疮、嗜酸细胞性食管炎、嗜酸性白细胞增多综合征、嗜酸细胞性肠胃炎、牙周疾病如慢性齿龈炎和牙周炎、泌尿生殖系统病症(如肾小球性肾炎、多囊性肾病、肾盂积水、肾衰竭、尿路梗阻、高尿酸血症等)、妇科病症(如外阴痛、阴道炎、骨腔病症等)、生殖疾病、泌尿疾病、线粒体相关病症、疼痛、偏头痛、血液疾病、精神障碍、口腔疾病(如口蹄疫)、肌肉骨骼疾病、眼部疾病、肾病(如肾病型胱氨酸病)、中毒(如酒精中毒、慢性水杨酸盐中毒)、皮肤搔痒症、皮肤角化病、皮肤病(如红斑鳞状、肥厚性皮肤病、流行性皮肤病、红斑痤疮、色素障碍、紫癜、痤疮、皮肤过敏、白斑病、大疱性皮肤病、表皮松解、硬皮病、湿疹、皮肤淋巴瘤)、肌肉萎缩病、肌肉病症、支气管疾病、血管疾病、子宫肌瘤、激素失调(如慢性疲劳综合征)、脱发、骨质疏松症、上呼吸道感染相关的炎症及佩吉特氏病(Paget's disease)。

[0281] 治疗代谢病症的方法

[0282] 本公开提供治疗个体的代谢病症的方法,所述方法包括向所述个体施用有效量的本公开的免疫调节组合物。代谢病症造成许多疾病,如肥胖相关代谢功能障碍、糖尿病、胰岛素抗性、葡萄糖代谢病症、低胰岛素血症、动脉粥样硬化、高胆固醇血症、局部缺血、代谢综合征、氧化应激、高血压、内分泌病症(艾迪生氏病(Addison'disease)、库兴氏病(Cushing's disease)、甲状腺机能亢进、甲状腺机能减退、垂体机能减退、多囊卵巢综合征等)、脂类代谢异常、肥胖相关病症(如骨丢失、体重增加等)、胰脏相关病症、线粒体疾病等。通过用本公开的免疫调节组合物调节先天性和适应性免疫机制(包括免疫细胞、细胞因子、抗体等),代谢疾病可得到预防和/或治疗。

[0283] 在一些情况下,治疗炎性病症的本公开方法包括向有此需要的个体施用免疫调节组合物,且还包括向所述个体施用有效量的至少一种另外的治疗剂、微生物组的一个或多个成员或益生菌。例如,所关注的治疗剂包括且不限于作为用于治疗心血管疾病的抗炎剂的那些试剂。这类试剂包括氨氯地平,用于降低血压和预防胸痛;依那普利,用于治疗高血压和一些类型的慢性心力衰竭;普伐他汀、阿托伐他汀及罗素伐他汀,用于治疗血脂异常和预防心血管疾病;血管紧张素转化酶(ACE)抑制剂(例如贝那普利、雷米普利等);血管紧张素II受体阻断剂(ARB)(例如坎地沙坦、氯沙坦等);β阻断剂(例如醋丁洛尔、比索洛尔、索他洛尔等);钙通道阻断剂(例如氨氯地平、维拉帕米等)等等。所关注的治疗剂的其它实例包括且不限于作为治疗糖尿病的抗炎剂的那些试剂。这类试剂包括靶向IKK-NF-κB途径的试剂;依那西普、英夫利昔单抗、阿达木单抗,其靶向TNF-α;阿那白滞素和卡那津单抗,其靶向IL-1β;托珠单抗,其靶向IL-6;AMP活化的蛋白激酶活化剂;sirtuin-1活化剂;雷帕霉素抑制剂的哺乳动物靶标;C-C基序趋化因子受体2拮抗剂等。在一些情况下,所关注的治疗剂包括且不限于作为用于治疗肥胖的抗炎剂的那些试剂。这类试剂包括氯卡色林;Qsymia™(Vivus);利拉鲁肽、丁氨苯丙酮、纳曲酮、氯卡色林、奥利司他、苯丁胺/托吡酯等。

[0284] 在一些情况下,所关注的治疗剂包括且不限于用于治疗代谢病症如糖尿病的那些试剂,包括胰岛素(例如短效、速效、中效和长效胰岛素)、胰淀素模拟药物(例如普兰林肽)、

α-葡糖苷酶抑制剂(例如阿卡波糖、米格列醇等)、双胍(例如二甲双胍等)、磺酰脲(例如优降糖、格列甲嗪等)、美格列脲(例如瑞格列奈)、D-苯丙氨酸衍生物(例如那格列奈)、噻唑烷二酮(例如罗格列酮、吡格列酮等)、DPP-4抑制剂(例如西他列汀、沙格列汀、利拉利汀等)、胰高血糖素样受体-1(GLP-1)激动剂(例如艾塞那肽、利拉鲁肽等)、钠葡萄糖转运蛋白-2(SGLT-2)抑制剂(例如坎格列净、达格列净等)等等。

[0285] 治疗神经障碍的方法

[0286] 本公开提供调节和/或调控炎性应答的方法,所述方法包括向有此需要的个体施用有效量的本公开的免疫调节组合物。炎性病状是以下许多神经障碍的原因:如阿尔茨海默氏病、抑郁症、注意缺陷多动障碍(ADHD)、心境障碍、精神分裂症、多发性硬化症、帕金森氏病、孤独症、肌萎缩性侧索硬化(ALS)、脑型疟疾、亨廷顿氏病、焦虑症、癫痫等。通过用本公开的免疫调节组合物调节先天性和适应性免疫机制(包括免疫细胞、细胞因子、抗体等),神经障碍可得到治疗。

[0287] 在一些情况下,治疗神经障碍的本公开方法包括向有此需要的个体施用免疫调节组合物,且还包括向所述个体施用有效量的至少一种另外的治疗剂、微生物组的一个或多个成员或益生菌。所关注的用于神经障碍的疾病缓解剂的非限制性实例包括乙酰胆碱酯酶抑制剂(例如多奈哌齐、卡巴拉汀等)、N-甲基,D-天冬氨酸受体(NMDAR)拮抗剂(例如美金刚胺、奈拉美生等)、多巴胺能药(例如甲基多巴肼/左旋多巴)、多巴胺激动剂(例如普拉克索、罗匹尼罗、阿朴吗啡等)、抗胆碱能药(例如三己芬迪、甲磺酸苯扎托品)、儿茶酚-邻甲基转移酶(COMT)抑制剂(例如恩他卡朋、托卡朋等)、抗惊厥剂(例如安定、巴氯芬、丹曲林、替扎尼定等)、疾病缓解剂;(例如特立氟胺、芬戈莫德、米托蒽醌、富马酸二甲酯、那他珠单抗等)。

[0288] 在一些情况下,所述方法包括向有此需要的个体施用有效量的呈疫苗形式的本公开的免疫调节组合物,所述疫苗包含将调节针对疾病相关蛋白(如阿尔茨海默氏病或痉挛性假硬化(CJD)所特有的淀粉样斑块)的免疫应答的抗原。

[0289] 预防或治疗免疫抑制和感染的方法

[0290] 本公开提供预防或限制由于病毒感染或由于中风及其它脑损伤后的感染所致的免疫缺陷/缺损/抑制的方法,所述方法包括向有此需要的个体施用本公开的免疫调节组合物。各种形式的病毒(例如HIV)感染、脑外伤(包括中风)造成长期全身性免疫抑制,由此导致较高的感染和死亡率。此外,肝脏非变异的NKT细胞已显示对改善全身性免疫抑制说来是重要的。本公开提出一种通过调节NK、NKT及其它免疫细胞预防这些患者中的全身性免疫抑制和感染的策略。

[0291] 在一些情况下,治疗免疫抑制、中风或脑外伤病症的本公开方法包括向有此需要的个体施用免疫治疗组合物,且还包括向所述个体施用有效量的至少一种另外的治疗剂。

[0292] 提高治疗性治疗的功效和/或降低其毒性的方法

[0293] 本公开还提供提高治疗性治疗的功效和/或降低其毒性、和/或预防抗药性和改变代谢的方法,优选地用抗感染药(如抗细菌剂、抗真菌剂或抗病毒剂)、抗癌剂、治疗性抗体、抗炎剂、代谢病症相关药物、免疫刺激剂、免疫调节化合物、免疫调控剂、Si RNA、包括益生菌和微生物组的治疗性微生物(活的、灭活的、热杀的、突变的、减毒的、基因工程化的)治疗或手术治疗,通过向个体、细胞或组织施用有效量的本公开的免疫调节组合物,优选为调控

免疫应答所需的量。

[0294] 在一些情况下，提高功效和降低毒性的本公开方法包括向有此需要的个体施用免疫调节组合物，且还包括向所述个体施用有效量的至少一种另外的治疗剂。

[0295] 合适的治疗剂和抗体的非限制性实例在上文的方法章节中有所描述。

[0296] 调节树突细胞的方法

[0297] 本公开提供一种调节树突细胞的方法，所述方法包括：a)使从个体处获得的树突细胞(DC)与包含以下的组合物接触：i)新月柄杆菌；和/或ii)抗原。使DC与CC和抗原在体外接触。DC与抗原和CC的接触调节DC上的抗原呈递，由此生成调节的DC群。在一些情况下，可使用如扩散、电穿孔、主动转运、脂质体融合、吞噬作用、超声处理等方法使抗原与DC接触。在一些情况下，所述方法还包括向DC由其获得的个体施用抗原呈递DC。在一些情况下，所述方法还包括向DC由其获得的个体施用抗原呈递DC与抗体、化疗剂或细胞因子的组合。向个体施用调节的DC可治疗个体中的疾病。

[0298] 合适的抗原如上所述。在一些情况下，使包含CC和抗原的组合物与DC接触；并且将CC-抗原-DC混合物孵育约30分钟至约48小时的一段时间，由此生成抗原呈递DC群。与在抗原呈递DC的初始群中的DC比例相比，本发明方法可将作为抗原呈递DC的DC的比例调节至少约25％、至少约50％、至少约75％、至少约2倍、至少约5倍、至少约10倍、至少约25倍、至少约50倍、至少约100倍或超过100倍。

[0299] 生成调控性免疫细胞的方法

[0300] 本公开提供一种生成调控性淋巴细胞如NK、NKT、γδT细胞、ILC、T细胞及B细胞的方法，所述方法包括：a)使从个体处获得的淋巴细胞(NK、NKT、γδT细胞、ILC、T细胞和/或B细胞)与包含以下的组合物在抗原呈递细胞存在或不存在下接触：i)新月柄杆菌；和/或ii)抗原。淋巴细胞与CC的接触产生调控性淋巴细胞群。在一些情况下，所述方法包括向细胞由其获得的个体施用调控性淋巴细胞，以便预防和/或治疗宿主中的疾病。在一些情况下，所述方法还包括向细胞由其获得的个体施用调控性淋巴细胞与抗体、化疗剂或细胞因子的组合，以便预防和/或治疗宿主中的疾病。

[0301] 治疗细胞内病原体感染的方法

[0302] 本公开提供预防和/或治疗个体中的胞内病原体(例如，病毒、分枝杆菌、细菌、寄生虫等)感染的方法，所述方法包括向所述个体施用有效量的本公开的免疫调节组合物。

[0303] 在一些情况下，治疗胞内病原体的本公开方法包括向有此需要的个体施用，且还包括向所述个体施用有效量的至少一种另外的治疗剂。

[0304] 出于研究、诊断和/或治疗目的来调节动物模型或细胞培养物中的免疫应答的方法

[0305] 本公开提供一种出于研究目的来调节动物模型中的免疫应答的方法。本公开还提供一种调节各种TLR、NLR、DC和/或效应淋巴细胞如NK、NKT、T和B细胞的方法，所述方法包括：a)使从个体处获得的效应细胞(NK、NKT、T和B细胞)与包含以下的组合物在抗原呈递细胞存在或不存在下接触：i)新月柄杆菌；和/或ii)抗原。效应淋巴细胞与CC的接触调节它们的活化，由此生成调控的效应淋巴细胞群。在一些情况下，所述方法包括通过鉴别和扩增特异性抗原反应性T细胞和/或B细胞来诊断疾病状况。在一些情况下，所述方法包括在体外鉴别和扩增特异性抗原反应性T细胞和/或B细胞以用于研究目的。在一些情况下，所述方法包

括向细胞由其获得的个体施用活化的效应淋巴细胞，以便预防和/或治疗宿主中的疾病。在一些情况下，所述方法包括激活TLR或NLR以用于研究和/或诊断目的。

[0306] 诱导干细胞的增殖、分化和/或调节的方法

[0307] 本公开提供一种在个体中诱导干细胞的增殖、分化和/或调节及恢复体内平衡的方法，所述方法包括向所述个体施用有效量的本公开的免疫调节组合物。本公开提供一种修饰干细胞的方法，所述方法包括使干细胞与包含新月柄杆菌的组合物接触，其中所述接触生成扩增的、分化的和/或调节的干细胞群。

[0308] 本公开还提供一种诱导干细胞的增殖、分化和/或调节的方法，所述方法包括使从个体处获得的干细胞与本公开的免疫调节组合物(例如，包含新月柄杆菌的免疫调节组合物)接触。干细胞与CC的接触造成它们的增殖和分化，由此生成扩增的、分化的和/或调节的细胞群。然后可将扩增的、分化的和/或调节的细胞群向干细胞由其所获得的个体施用。

[0309] 在一些实施方案中，本公开的诱导干细胞的增殖、分化和/或调节的方法包括：a)从个体处获得干细胞；b)使干细胞在体外与CC接触，由此生成扩增的、分化的和/或调节的细胞群；以及c)向所述个体施用所扩增、分化和/或调节的细胞群。

[0310] 在一些实施方案中，在个体中诱导干细胞的增殖、分化和/或调节的本公开方法包括向所述个体施用有效量的本公开的免疫调节组合物。在一些情况下，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时有效诱导造血干细胞的增殖、分化和/或调节并恢复体内平衡的量。例如，在一些情况下，与在不存在免疫调节组合物治疗下的个体相比，本公开的免疫调节组合物的有效量为当以单剂量或多剂量施用时在个体中有效诱导造血干细胞的增殖、分化和/或调节并恢复体内平衡至少10％、至少15％、至少20％、至少25％、至少30％、至少35％、至少40％、至少45％、至少50％、至少75％、至少100％(或2倍)、至少2.5倍、至少5倍、至少10倍、大于10倍、至少15倍、至少20倍、至少25倍、至少50倍、至少100倍或大于100倍的量。

[0311] 递送治疗性分子的方法

[0312] 本公开提供一种递送如蛋白质、肽、siRNA、碳水化合物、大分子等治疗性分子的方法，其中新月柄杆菌可充当递送治疗性分子的载体和/或递送媒介物。由于非遗传修饰(GM)，如静电和疏水性相互作用，分子与新月柄杆菌表面的结合可使得新月柄杆菌能充当载体和/或递送媒介物。而且，由于生物粘附/粘膜粘附，新月柄杆菌可促进在粘膜表面处通过M细胞转运的递送摄取。

[0313] 制剂、剂量和施用途径

[0314] 本公开的免疫调节组合物可包含一种或多种药学上可接受的赋形剂；并且可以多种方式中的任一种配制，配制方式可取决于例如施用途径。药学上可接受的赋形剂为本领域技术人员所知，并且已在多个出版物中有详细描述，包括例如A.Gennaro(1995)"Remington:The Science and Practice of Pharmacy"，第19版，Lippincott，Williams，& Wilkins。合适的赋形剂媒介物包括例如：水、盐水、葡萄糖、甘油、乙醇、惰性蛋白质、亲水性聚合物、氨基酸、脂肪酸、表面活性剂、非离子型表面活性剂、碳水化合物、糊精、多元醇、螯合剂等、及其组合。另外，如果需要的话，媒介物可含有少量辅助物质，如润湿剂或乳化剂或pH缓冲剂。制备这类剂型的实际方法是已知的或将为本领域技术人员显而易见。参见，例如Remington's Pharmaceutical Sciences，Mack Publishing Company，Easton，

Pennsylvania,第17版,1985;Remington:The Science and Practice of Pharmacy,A.R.Gennaro,(2000)Lippincott,Williams&Wilkins。

[0315] 免疫调节组合物可掺入到多种制剂中以供治疗性给药。更具体地说,免疫调节组合物可通过与适当的药学上可接受的载体、盐、防腐剂、缓冲剂或稀释剂组合而配制成药物组合物,并且可配制成呈固体、半固体、液体、冻干、冷冻干燥或气态形式的制剂,如片剂、胶囊、粉剂、颗粒剂、膏剂、溶液、栓剂、注射剂、皮肤贴剂、吸入剂及气溶胶。在其它实施方案中,制剂包含胶态递送系统,其包括例如脂质体、纳米颗粒、纳米乳液、纳米胶囊、微球及聚合物。

[0316] 在药物剂型中,免疫调节组合物可单独或以与其它药学活性化合物适当联合及组合形式施用。免疫调节组合物、抗原、佐剂和/或治疗性药物可并行、同时、依次或在不同时间下,在相同或不同的部位处并经由不同途径施用。以下方法和赋形剂仅为示例性的且决不限制。

[0317] 对于口服制剂,免疫调节组合物可单独或以与以下适当添加剂的组合形式使用以制造片剂、粉剂、颗粒剂或胶囊,例如,与常规的添加剂,如乳糖、甘露糖醇、玉米淀粉或马铃薯淀粉;与粘合剂,如结晶纤维素、纤维素衍生物、阿拉伯胶、玉米淀粉或明胶;与崩解剂,如玉米淀粉、马铃薯淀粉或羧甲基纤维素钠;与润滑剂,如滑石或硬脂酸镁;并且如果需要的话,与稀释剂、缓冲剂、润湿剂、防腐剂及调味剂。

[0318] 免疫调节组合物可通过将组合物溶解、悬浮或乳化于含水或非水溶剂中而配制成供施用的液体制剂,所述溶剂如植物或其它类似油、合成脂肪族酸甘油酯、高级脂肪酸或丙二醇的酯;并且如果需要的话,用常规添加剂,如增溶剂、等渗剂、悬浮剂、乳化剂、稳定剂及防腐剂。

[0319] 免疫调节组合物可以气溶胶制剂形式使用以便经由吸入施用。本公开的免疫调节组合物可被配制到加压可接受的推进剂中,如二氯二氟甲烷、丙烷、氮气等。

[0320] 此外,免疫调节组合物可通过与多种基质如乳化基质或水溶性基质混合而制成栓剂。免疫调节组合物可经由栓剂直肠施用。栓剂可包括媒介物,如可可脂、碳蜡和聚乙二醇,其在体温下融化,而在室温下凝固。

[0321] 本公开的免疫调节组合物也可以脂质体或脂质体聚合凝胶形式施用。脂质体可通过以下多种途径给予:经口、经鼻、胃肠外、经皮、经吸入等。如本领域中已知,脂质体来源于磷脂或其它脂质物质。脂质体通过将单层或多层水合液体晶体分散在含水介质中而形成。可使用能够形成脂质体的任何无毒的、生理学上可接受的和可代谢的脂质。呈脂质体形式的本组合物除本公开的免疫调节组合物之外还可含有稳定剂、防腐剂、赋形剂等中的一种或多种。示例性脂质为天然和合成的磷脂和磷脂酰胆碱(卵磷脂)。脂质体可具有在小于100nm至几微米范围内的尺寸。形成脂质体的方法是本领域中已知的。例如,Prescott编著,MethodsinCell Biology,第XIV卷,Academic Press,New York,N.Y.(1976),第33页及以下。

[0322] 可提供用于口服或直肠施用的单位剂型,如糖浆剂、酏剂、乳液和悬浮液,其中每个剂量单位(例如茶匙、汤匙、片剂或栓剂)含有预定量的含有一种或多种活性剂的组合物。类似地,用于注射或静脉内施用的单位剂型可包含呈在无菌水、生理盐水或另一种药学上可接受的载体中的溶液形式的免疫调节组合物。

[0323] 本发明的免疫调节组合物可被配制用于局部施用。局部施用包括施用于皮肤或粘膜，包括肺、眼、鼻和耳的表面。合适的局部制剂包括例如皮肤贴剂制剂、经皮贴剂制剂、微阵列、霜剂、洗剂、凝胶制剂、粉剂、膏剂、糊剂、鼻内滴剂或凝胶。

[0324] 膏剂为半固体制剂，其通常是基于矿脂或其它石油衍生物。合适的膏剂包括油性基质；可乳化基质；乳液基质；及水溶性基质。油性膏剂基质包括例如植物油、从动物处获得的脂肪、及从石油处获得的半固体烃类。可乳化的膏剂基质(也称为吸收性膏剂基质)几乎不含或不含水并且包括例如硫酸羟基硬脂、无水羊毛脂及亲水性矿脂。乳液膏剂基质为油包水(WIO)乳液或水包油(OIW)乳液，并且包括例如十六醇、单硬脂酸甘油酯、羊毛脂及硬脂酸。示例性水溶性膏剂基质是由不同分子量的聚乙二醇来制备。

[0325] 洗剂是施用于皮肤表面勿需摩擦的制剂，且通常是液体或半液体制剂，其中固体颗粒包括活性剂，存在于水或醇基质中。洗剂通常是固体悬浮液，出于本发明的目的，优选含有水包油型的液体油状乳液。洗剂可用于治疗大面积身体部位，因为偏液态的组合物更容易施用。洗剂可含有悬浮剂，以实现更好的分散，并且还含有可用于使活性剂定位并保持与皮肤接触的化合物，例如甲基纤维素、羧甲基纤维素钠等。与本发明结合使用的洗剂制剂的一个实例含有与亲水性矿脂混合的丙二醇，这种矿脂例如可以从Beiersdorf,Inc.(Norwalk,Coon.)以商标名Aquaphor®出售而获得。

[0326] 合适的霜剂可为粘性液体或半固体乳液，呈水包油或油包水。霜剂基质是可水洗的，并且含有油相、乳化剂和水相。油相有时也称为“内部”相，其通常由矿脂和脂肪醇如十六烷基或十八烷基醇构成；水相尽管通常不是必须的，但其体积超过油相，且通常含有湿润剂。如Remington,同上所说明的霜剂制剂中的乳化剂通常是非离子、阴离子、阳离子或两性表面活性剂。

[0327] 可使用凝胶制剂。凝胶为半固体、悬浮液/型系统。单相凝胶含有基本上均匀地分布在载液中的有机大分子，其可为含水的，但也可含有乙醇且任选地含有油。

[0328] 局部制剂也可使用常规的“经皮”型贴剂递送给皮肤，其中所述试剂(免疫调节组合物)包含在层状结构内，该层状结构充当附着于皮肤的递送装置。在这类结构中，免疫调节组合物包含在上背衬层下面的层或“储库”中。层状结构可含有单个储库，或其可含有多个储库。在一个实施方案中，储库包含用于使系统在药物递送期间粘附到皮肤上的药学上可接受的接触粘合材料的聚合物基体。合适的皮肤接触粘合材料的实例包括但不限于聚乙烯、聚硅氧烷、聚异丁烯、聚丙烯酸酯、聚氨酯等。所选的具体聚合粘结剂将取决于具体的免疫调节组合物、媒介物等，即，粘结剂必须与含药物的组合物的所有组分相容。在一个替代实施方案中，含有免疫调节组合物的储库和皮肤接触粘结剂可作为独立和独特的层存在，同时粘结剂在储库的下面，在此情况下，所述层可为如上所述的聚合物基体，或其可为液体或水凝胶储库，或者可采用一些其他形式。

[0329] 如本文所用的术语“单位剂型”是指适合人和动物受试者用的单一剂量的物理上离散单位，每一单位含有预定量的活性剂(例如，CC；抗原等)和药学上可接受的稀释剂、载体或媒介物，该预定量经计算足以产生所需效果。活性剂的规格取决于所用的具体化合物和有待实现的效果、以及宿主中的每种化合物相关的药物动力学。

[0330] 也可使用其它施用模式。例如，免疫调节组合物可以栓剂形式配制，且在一些情况下，为气溶胶和鼻内组合物。对于栓剂，媒介物组合物将包括传统的粘合剂和载体，如聚二

醇或甘油三酯。这类栓剂可由含有在约0.5％至约10％(w/w)或约1％至约2％范围内的活性成分的混合物形成。

[0331] 鼻内制剂通常将包括既不对鼻粘膜造成刺激又不明显妨碍纤毛功能的媒介物。可采用稀释剂，如水、水性盐水或其它已知物质。鼻腔制剂还可含有防腐剂，如但不限于氯丁醇和杀藻胺。还可含有表面活性剂，增强鼻粘膜对本发明蛋白质的吸收。

[0332] 免疫调节组合物可作为可注射剂施用。通常，可注射组合物是作为液体溶液或悬浮液来制备；也可制备注射前适于液体媒介物溶液或液体媒介物悬浮液的固体形式。制剂也可被乳化或者活性成分被包裹在脂质体媒介物中。

[0333] 合适的赋形剂媒介物为例如水、盐水、葡萄糖、甘油、乙醇等、及其组合。另外，如果需要的话，媒介物可含有少量辅助物质，如润湿剂或乳化剂或pH缓冲剂。制备这类剂型的实际方法是已知的或将为本领域技术人员显而易见。参见，例如Remington's Pharmaceutical Sciences,Mack Publishing Company,Easton,Pennsylvania,第17版,1985;Remington:The Science and Practice of Pharmacy,A.R.Gennaro,(2000)Lippincott,Williams&Wilkins。在任何情况下，有待施用的组合物或制剂含有的活性剂(例如,CC;抗原等)的量应足以在所治疗的受试者中实现所需效果。

[0334] 药学上可接受的赋形剂如媒介物、佐剂、盐、载体或稀释剂容易为公众所获得。此外，药学上可接受的助剂物质，如pH调节和缓冲剂、渗透压调节剂、稳定剂、乳化剂、表面活性剂、防腐剂、氨基酸、脂肪酸、润湿剂等等，同样容易为公众所获得。

[0335] 口服制剂

[0336] 在一些实施方案中，免疫调节组合物被配制以便向需要所述免疫调节组合物的个体经口递送。

[0337] 对于经口递送，在一些实施方案中，包含免疫调节组合物的本发明制剂包含肠溶性包衣材料。合适的肠溶性包衣材料包括醋酸羟丙基甲基纤维素琥珀酸酯(HPMCAS)、羟丙基甲基纤维素邻苯二甲酸酯(HPMCP)、醋酸纤维素邻苯二甲酸酯(CAP)、醋酸聚乙烯邻苯二甲酸酯(PVPA)、Eudragit™及虫胶。

[0338] 合适的口服制剂还包括用任何以下物质来配制的免疫调节组合物：微颗粒(参见，例如美国专利号6,458,398)；生物可降解的大分子单体(参见，例如美国专利号6,703,037)；生物可降解的水凝胶(参见，例如Graham和McNeill(1989)Biomaterials 5:27-36)；生物可降解的微粒载体(参见，例如美国专利号5,736,371)；生物可吸收的内酯聚合物(参见，例如美国专利号5,631,015)；缓慢释放的蛋白质聚合物(参见，例如美国专利号6,699,504;Pelias Technologies,Inc.)；聚(丙交酯-共-乙交酯/聚乙二醇嵌段共聚物(参见，例如美国专利号6,630,155;Atrix Laboratories,Inc.)；包含生物相容性聚合物及分散在聚合物内的金属阳离子稳定剂的颗粒的组合物(参见，例如美国专利号6,379,701;Alkermes Controlled Therapeutics,Inc.)；以及微球(参见，例如美国专利号6,303,148;Octoplus,B.V.)。

[0339] 合适的口服制剂还包括用任何以下物质配制的免疫调节组合物：载体如Emisphere®(Emisphere Technologies,Inc.)；TIMERx,即合并有黄原胶和刺槐豆胶的亲水性基体，其在葡萄糖存在下于水中形成强粘合剂(Penwest)；Geminex™(Penwest)；Procise™(GlaxoSmithKline)；SAVIT™(Mistral Pharma Inc.)；RingCap™(Alza Corp.)；

Smartrix® (Smartrix Technologies,Inc.);SQZgel™(MacroMed,Inc.);Geomatrix™ (Skye Pharma,Inc.);Oros®Tri-layer(Alza Corporation);等等。

[0340] 同样适用的是以下制剂,如在美国专利号6,296,842(Alkermes Controlled Therapeutics,Inc.);美国专利号6,187,330(Scios,Inc.)等中所述的那些。

[0341] 在本文中同样适用的是包含肠吸收增强剂的制剂。合适的肠吸收增强剂包括但不限于钙螯合剂(例如柠檬酸盐、乙二胺四乙酸);表面活性剂(例如十二烷基硫酸钠、胆汁盐、棕榈酰肉毒碱及脂肪酸钠盐);毒素(例如闭锁小带毒素);等等。

[0342] 合适的口服制剂还包括配制成以下形式的免疫调节组合物:食品增补剂(例如营养品、酸奶、冻酸奶、奶粉、乳酪、能量棒、饮品、益生元、共生菌、副益生菌)等。

[0343] 控制释放制剂

[0344] 在一些实施方案中,将免疫调节组合物以控制释放制剂形式配制。

[0345] 控制释放可意谓许多延长释放剂型中的任一种。出于本发明的目的,下列术语可被视为基本上等同于控制释放:连续释放、控制释放、延缓释放、贮库、逐渐释放、长期释放、程序化释放、延长释放、按比例释放、延迟释放、长效、延缓、缓慢释放、间隔释放、持续释放、定时包衣(time coat)、定时释放、延缓作用、延长作用、按时分层作用、长效、延长作用、重复作用、缓慢作用、持续作用、持续作用药物及长期释放。这些术语的进一步论述可见于Lesczek Krowczynski,Extended-Release Dosage Forms,1987(CRC Press,Inc.)中。

[0346] 各种控制释放技术涉及到非常广泛的药物剂型。控制释放技术包括但不限于物理系统和化学系统。

[0347] 物理系统包括但不限于带速度控制膜的储库系统,如微囊化、粗囊化和膜系统;不带速度控制膜的储库系统,如中空纤维、超微孔三醋酸纤维素、及多孔聚合基材和泡沫;单片(monolithic)系统,包括物理溶于非多孔的、聚合的或弹性的基体(例如,不易受侵蚀的、易受侵蚀的、环境剂进入和可降解的)的那些系统,和物理分散于非多孔的、聚合的或弹性的基体(例如,不易受侵蚀的、易受侵蚀的、环境剂进入和可降解的)材料;层状结构,包括化学上类似于或不类似于外控制层的储库层;及其它物理方法,如渗透泵、或在离子交换树脂上的吸收。

[0348] 化学系统包括但不限于聚合物基体的化学侵蚀(例如,异质或同质侵蚀)、或聚合物基体的生物侵蚀(例如,异质或同质的)。用于控制释放的系统类别的另外论述可见于Agis F.Kydonieus,Controlled Release Technologies:Methods,Theory and Applications,1980(CRC Press,Inc.)中。

[0349] 存在许多控制释放药物制剂,其被开发出来用于经口施用。这些制剂包括但不限于:渗透压控制的胃肠递送系统;流体压力控制的胃肠递送系统;膜渗透控制的胃肠递送系统,其包括微孔膜渗透控制的胃肠递送装置;抗胃液的肠靶向控制释放胃肠递送装置;凝胶扩散控制的胃肠递送系统;以及离子交换控制的胃肠递送系统,包括阳离子和阴离子药物。关于控制释放药物递送系统的另外信息可见于Yie W.Chien,Novel Drug Delivery Systems,1992(Marcel Dekker,Inc.)中。现将更详细地论述其中一些制剂。

[0350] 将肠溶包衣涂敷到片剂上,以免活性剂在胃中释放,从而降低产生不希望的副作用的危险或者保持药物的稳定性,否则这些药物由于暴露于胃环境而可能发生降解。用于这个目的的大多数聚合物是多酸,它们根据或由于以下事实发挥作用:它们在含水介质中

的溶解度取决于pH值，且它们需要具有比胃内通常遇到的pH要高的pH的条件。

[0351] 口服控制释放结构的一个示例性类型是固体或液体剂型的肠溶包衣。肠溶包衣被设计在肠液中崩解以便于快速吸收。掺入到具有肠溶包衣的制剂中的活性剂的吸收延迟取决于通过胃肠道的移动速率，所以胃排空的速率是一个重要因素。一些研究者已经报道，多单位型剂型如颗粒剂可能优于单个单位型。

[0352] 合适的肠溶包衣剂包括但不限于：羟丙基甲基纤维素邻苯二甲酸酯、甲基丙烯酸-甲基丙烯酸酯共聚物、聚乙烯醋酸酯-邻苯二甲酸酯及醋酸邻苯二甲酸纤维素。

[0353] 另一种类型的有用的口服控制释放结构为固态分散体。固态分散体可被定义为一种或多种活性成分在呈固态的惰性载体或基体中的分散体，通过熔化(熔融)法、溶剂法或熔化-溶剂法来制备。

[0354] 可用于固态分散体的载体的实例包括但不限于水溶性聚合物，如聚乙二醇、聚乙烯吡咯烷酮及羟丙基甲基纤维素。替代的载体包括磷脂酰胆碱。磷脂酰胆碱为两性但水不溶性脂质，其可改善呈非晶态的其它不溶性活性剂在磷脂酰胆碱固态分散体中的溶解度。

[0355] 其它载体包括聚氧乙烯氢化蓖麻油。免疫调节组合物可包括在具有肠溶性聚合物如羟丙基甲基纤维素邻苯二甲酸酯和非肠溶性聚合物如羟丙基甲基纤维素的固态分散体系统中。另一种固态分散体剂型包括将所关注的药物(例如活性剂)与乙基纤维素和硬脂酸以不同比率掺合。

[0356] 存在通常已知用于制备固态分散体的各种方法。这些方法包括但不限于熔化法、溶剂法及熔化-溶剂法。

[0357] 可注射微球为另一种控制释放剂型。可注射微球可通过非水相分离技术和喷雾干燥技术来制备。微球可使用聚乳酸或共聚(乳酸/羟基乙酸)来制备。

[0358] 可使用的其它控制释放技术包括但不限于：SODAS(Spheroidal Oral Drug Absorption System)、INDAS(Insoluble Drug Absorption System)、IPDAS(Intestinal Protective Drug Absorption System)、MODAS(Multiporous Oral Drug Absorption System)、EFVAS(Effervescent Drug Absorption System)、PRODAS(Programmable Oral Drug Absorption System)及DUREDAS(Dual Release Drug Absorption System)，可从Elan Pharmaceutical Technologies获得。SODAS是利用控制释放珠的多颗粒剂型。INDAS是为提高难溶药物的溶解度而设计的一系列药物递送技术。IPDAS是利用高密度控制释放珠与立即释放颗粒的组合的多颗粒片剂形式。MODAS是控制释放单一单位剂型。每个片剂是由被半透性多产膜围绕的内核组成，该半透膜控制药物释放速率。EFVAS是泡腾药物吸收系统。PRODAS是采用立即释放与控制释放微型片剂的组合的一系列多颗粒制剂。DUREDAS是在一种剂型内提供双重释放速率的双层片剂制剂。虽然这些剂型为本领域技术人员所知，但现将更详细地论述其中某些剂型。

[0359] 本公开的免疫调节组合物可掺入到上述控制释放剂型或其它常规剂型的任一种中。每剂所包含的活性剂的量可被调节，以满足个体患者的需要和适应症。本领域技术人员在阅读本公开后将容易知晓如何调节活性剂在控制释放制剂中的水平和释放速率，以便优化活性剂的递送及其生物利用度。

[0360] 吸入性制剂

[0361] 在一些实施方案中，本公开的免疫调节组合物将藉助于用于吸入途径的药物递送

系统向患者施用。免疫调节组合物可以适合吸入施用的形式来配制。吸入施用途径的优点在于:吸入性药物可绕过血脑屏障。药物递送系统是一种适用于呼吸疗法的系统,其将活性剂递送至支气管的粘膜内衬。也可使用依赖压缩气体的驱动力以将免疫调节组合物从容器中喷出的系统。气溶胶或加压包可用于此目的。

[0362] 如本文所用,术语“气溶胶”是依据它的常规含义来使用,意指被加压推进气体携载至治疗性施加位置的极细微液态或固态颗粒。当采用药物气溶胶时,气溶胶含有治疗活性化合物(例如活性剂),其可溶解、悬浮或乳化于流体载体和推进剂的混合物中。气溶胶可呈溶液、悬浮液、乳液、粉剂或半固体制剂形式。气溶胶可作为精细的固体颗粒或作为液体薄雾经由患者的呼吸道施用。可利用本领域技术人员已知的各种类型的推进剂。合适的推进剂包括但不限于烃类或其它合适的气体。在加压气溶胶的情况下,剂量单位可通过提供递送计量数量的值来确定。

[0363] 免疫调节组合物还可被配制用于以喷雾器来递送,喷雾器是一种在气体中生成基本均匀大小的极精细液体颗粒的仪器。例如,含有免疫调节组合物的液体是以液滴形式分散。小液滴可由空气流携带通过喷雾器的出口管。所生成的薄雾渗入患者的呼吸道中。

[0364] 存在几种不同类型的吸入方法,这些方法可结合本公开的免疫调节组合物使用。免疫调节组合物可用低沸点推进剂来配制。这类制剂通常经由常规的定量吸入器(MDI)来施用。或者,免疫调节组合物可以含水或乙醇溶液形式来配制并由常规的喷雾器递送。在一些实施方案中,使用如美国专利5,497,763;5,544,646;5,718,222;和5,660,166中所公开的装置和系统将这类溶液制剂雾化。免疫调节组合物可被配制成干燥粉末制剂。这类制剂可通过在产生粉末的气溶胶薄雾之后简单地吸入干燥粉末制剂来施用。进行此操作的技术描述于1998年7月7日公布的美国专利5,775,320和1998年4月21日公布的美国专利5,740,794中。

[0365] 在一些实施方案中,本公开的免疫调节组合物将被配制用于经阴道递送。用于阴道内施用的本发明免疫调节组合物可被配制成阴道内生物粘附片剂、阴道内生物粘附微颗粒、阴道内霜剂、阴道内洗剂、阴道内泡沫剂、阴道内膏剂、阴道内糊剂、阴道内溶液或阴道内凝胶。

[0366] 在一些实施方案中,本发明的免疫调节组合物将被配制用于经直肠递送。用于直肠内施用的本发明制剂包含本发明免疫调节组合物,该组合物被配制成直肠内生物粘附片剂、直肠内生物粘附微颗粒、直肠内霜剂、直肠内洗剂、直肠内泡沫剂、直肠内膏剂、直肠内糊剂、直肠内溶液或直肠内凝胶。本公开的免疫调节组合物可用改善对粘膜的粘附的试剂来配制:如粘膜粘附剂、生物粘附剂、颗粒、微球或脂质体。

[0367] 本发明免疫调节组合物可包含以下一种或多种:赋形剂(例如蔗糖、淀粉、甘露糖醇、山梨糖醇、乳糖、葡萄糖、纤维素、滑石、磷酸钙或碳酸钙)、粘合剂(例如纤维素、甲基纤维素、羟甲基纤维素、聚丙基吡咯烷酮、聚乙烯吡咯烷酮、明胶、阿拉伯胶、聚(乙二醇)、蔗糖或淀粉)、崩解剂(例如淀粉、羧甲基纤维素、羟丙基淀粉、低取代的羟丙基纤维素、碳酸氢钠、磷酸钙或柠檬酸钙)、润滑剂(例如硬脂酸镁、轻质无水硅酸、滑石或十二烷基硫酸钠)、调味剂(例如柠檬酸、薄荷醇、甘氨酸或橙粉)、防腐剂(例如苯甲酸钠、亚硫酸氢钠、对羟基苯甲酸甲酯或对羟基苯甲酸丙酯)、稳定剂(例如柠檬酸、柠檬酸钠或乙酸)、悬浮剂(例如甲基纤维素、聚乙烯吡咯烷酮或硬脂酸铝)、分散剂(例如羟丙基甲基纤维素)、稀释剂(例如

水)、以及基质蜡(例如可可脂、白凡士林或聚乙二醇)。

[0368] 包含免疫调节组合物的片剂可用合适的成膜剂涂布,例如羟丙基甲基纤维素、羟丙基纤维素或乙基纤维素,可向其中任选地添加合适的赋形剂,例如,软化剂,如甘油、丙二醇、酞酸二乙酯或甘油三醋酸;填充剂,如蔗糖、山梨糖醇、木糖醇、葡萄糖或乳糖;着色剂,如氢氧化钛;等等。

[0369] 剂量

[0370] 本公开的免疫调节组合物的剂量可根据以下因素而变化:如有待实现的临床目标、所治疗个体的年龄、所治疗个体的身体状况等。

[0371] 本公开的免疫调节组合物可包含每单位剂型约10^3CC至每单位剂型约10^{20}CC之量的CC。例如,本公开的免疫调节组合物可包含以下量的CC:每单位剂型约10^3CC至每单位剂型约10^4CC、每单位剂型约10^4CC至每单位剂型约10^5CC、每单位剂型约10^5CC至每单位剂型约10^6CC、每单位剂型约10^6CC至每ml约10^7CC、每单位剂型约10^8CC至每单位剂型约10^9CC、每ml约10^9CC至每单位剂型约10^{10}CC、每单位剂型约10^{15}CC至每单位剂型约10^{20}CC、或大于每单位剂型10^{20}CC。

[0372] 例如,本公开的免疫调节组合物可包含每ml约10^3CC至每ml约10^{20}CC之量的CC。例如,本公开的免疫调节组合物可包含以下量的CC:每ml约10^3CC至每ml约10^4CC、每ml约10^4CC至每ml约10^5CC、每ml约10^5CC至每ml约10^6CC、每ml约10^6CC至每ml约10^7CC、每ml约10^8CC至每ml约10^9CC、每ml约10^9CC至每ml约10^{10}CC、每ml约10^{15}CC至每ml约10^{20}CC、或大于每ml 10^{20}CC。

[0373] 本公开的免疫调节组合物可包含每单位剂型约10^2至约10^{20}个集落形成单位(cfu)之量的CC;举例来说,本公开的免疫调节组合物可包含每单位剂型以下量的CC:约10^2至约10^3、约10^3至约10^5、约10^5至约10^7、约10^7至约10^9、约10^9至约10^{11}、约10^{11}至约10^{13}、约10^{13}至约10^{15}、约10^{15}至约10^{18}、或约10^{18}至约10^{20}cfu。单位剂型可为以单剂量施用的量;举例来说,单位剂型可为0.5ml、1.0ml、或适合以单剂量施用的其它体积。

[0374] 本公开的免疫调节组合物可包含每mg约10^3CC至每mg约10^{12}CC之量的CC。例如,本公开的免疫调节组合物可包含以下量的CC:每mg约10^3CC至每mg约10^4CC、每mg约10^4CC至每mg约10^5CC、每mg约10^5CC至每mg约10^6CC、每mg约10^6CC至每mg约10^7CC、每mg约10^8CC至每mg约10^9CC、每mg约10^9CC至每mg约10^{10}CC、每mg约10^{10}CC至每mg约10^{11}CC、或每mg约10^{11}CC至每mg约10^{12}CC。

[0375] 本公开的免疫调节组合物可包含每克约10^3CC至每克约10^{15}CC之量的CC。例如,本公开的免疫调节组合物可包含以下量的CC:每克约10^3CC至每克约10^4CC、每克约10^4CC至每克约10^5CC、每克约10^5CC至每克约10^6CC、每克约10^6CC至每克约10^7CC、每克约10^8CC至每克约10^9CC、每克约10^9CC至每克约10^{10}CC、每克约10^{10}CC至每克约10^{11}CC、每克约10^{11}CC至每克约10^{12}CC、每克约10^{12}CC至每克约10^{13}CC、每克约10^{13}CC至每克约10^{14}CC、或每克约10^{14}CC至每克约10^{15}CC。

[0376] 本公开的免疫调节组合物可包含约10^2至约10^{20}cfu/ml之量的CC;举例来说,本公开的免疫调节组合物可包含以下量的CC:约10^2至约10^3、约10^3至约10^5、约10^5至约10^7、约10^7至约10^9、约10^9至约10^{11}、约10^{11}至约10^{13}、约10^{13}至约10^{15}、约10^{15}至约10^{18}、或约10^{18}至约10^{20}cfu/ml。

[0377] 在一些实施方案中，施用多剂量的本公开的免疫调节组合物。本公开的免疫调节组合物的施用频繁可根据以下多种因素中的任何而变化，例如，症状的严重性等。例如，在一些实施方案中，本公开的免疫调节组合物可如下施用：每月一次、每月两次、每月三次、每隔一周(qow)、每周一次(qw)、每周两次(biw)、每周三次(tiw)、每周四次、每周五次、每周六次、每隔一天(qod)、每天(qd)、每天两次(qid)、或每天三次(tid)。

[0378] 本公开的免疫调节组合物的施用持续时间(例如，施用本公开的免疫调节组合物所经的时间段)可根据以下多种因素中的任何而变化，例如，患者应答等。例如，本公开的免疫调节组合物可经以下范围内的时间段施用：约单的小时至一天、约一天至约一周、约两周至约四周、约一个月至约两个月、约两个月至约四个月、约四个月至约六个月、约六个月至约八个月、约八个月至约1年、约1年至约2年、或约2年至约4年或更久。

[0379] 当免疫调节组合物包含抗原时，抗原的剂量被选为有效并调节免疫应答而无显著不良副作用的量。所述量可例如根据所采用的特异性抗原、施用途径等而变化。当免疫调节组合物包含抗原时，抗原的剂量可在每单位剂型1ng至每单位剂型约100mg范围内，例如，每单位剂型约1ng至约25ng、约25ng至约50ng、约50ng至约100ng、约100ng至约250ng、约250ng至约500ng、约500ng至约750ng、约750ng至约1μg、约1μg至约25μg、约25μg至约50μg、约50μg至约100μg、约100μg至约250μg、约250μg至约500μg、约500μg至约750μg、约750μg至约1mg、约1mg至约25mg、约25mg至约50mg、或约50mg至约100mg。

[0380] 施用途径

[0381] 使用适合于药物递送的任何可利用的方法和途径向个体施用本公开的免疫调节组合物，包括体内和离体方法以及全身和局部施用途径。

[0382] 常规的和药学上可接受的施用途径包括鼻内、肌内、气管内、皮下、皮内、结节内、透皮、经皮、肿瘤内、局部施用、静脉内、囊泡内、经直肠、经鼻、经口及其它肠内和胃肠外施用途径。施用途径如果需要的话可被组合或根据试剂和/或所需效果来调整。组合物可以单剂量或多剂量施用。

[0383] 可使用适合于常规药物递送的任何可利用的常规方法或途径向宿主施用本公开的免疫调节组合物，包括全身或局部途径。一般说来，预期施用途径包括但不一定限于肠内、胃肠外或吸入途径。

[0384] 除吸入施用以外的胃肠外施用途径包括但不一定限于局部、经皮、皮下、肌内、皮内、淋巴内、眶内、囊内、脊柱内、胸骨内、颅内、囊泡内及静脉内途径，即，除经由消化道以外的任何施用途径。可进行胃肠外施用以实现免疫调节组合物的全身或局部递送。当需要全身递送时，施用通常包括药物制剂的侵入式或全身吸收的局部或粘膜施用。

[0385] 本公开的免疫调节组合物还可通过肠内施用递送给受试者。肠内施用途径包括但不必限于经口和经直肠(例如，使用栓剂)递送。

[0386] 本公开的免疫调节组合物也可经由粘膜递送途径递送给受试者。粘膜递送途径包括经鼻、颊内、舌下、经阴道、经眼部和经直肠施用途径。

[0387] 在某些实施方案中，本公开的免疫调节组合物经由不同途径的组合以下文所示的顺序向受试者施用：

[0388] i.全身、粘膜；

[0389] ii.全身、全身、粘膜、粘膜；

[0390] iii.全身、粘膜、全身；

[0391] iv.粘膜、粘膜、全身、全身；

[0392] v.粘膜、全身、全身；

[0393] vi.粘膜、全身、粘膜，举例来说。

[0394] 当全身或粘膜施用本公开的免疫调节组合物一次以上时，两次或更多次全身或粘膜施用可通过相同的全身(例如，两次肌内注射)或粘膜途径(两次IN/SL施用)或不同(例如，一次肌内注射和一次静脉内注射；一次IN施用和一次SL施用)途径进行。

[0395] 使用以下任何可利用的方法、递送或装置向个体施用本公开的免疫调节组合物：如疫苗贴剂、针、显微针(空心或实心)、滴剂、糖浆剂、片剂、胶囊、吸移管、剂量喷雾泵、鼻滴管、吸入装置、液体或干燥粉末、悬浮液或溶液、喷洒器、Accuspray™、热响应凝胶、喷射注射器、Nasovak™、Bespak™、膏剂、洗剂、栓剂、凝胶等。

[0396] 合适的施用途径在本领域中是已知的；任何已知的施用途径可联合施用本公开的免疫调节组合物来使用。参见，例如Nursing Drug Guide:Nursing Drug Handbook(2015)第36版,Lippincott。

[0397] 适合治疗的个体

[0398] 适合使用本公开方法治疗的个体包括人；非人哺乳动物；鱼；及鸟。在下文论述的以上实施方案的任一个中，使用本发明方法治疗的个体可为非人哺乳动物，如家畜(例如猪、绵羊、山羊、牛、马、公山羊、羊、牛等)；哺乳动物宠物(例如猫、狗、马等)；鸟，如鸡、母鸡、火鸡、鹅、鹌鹑、鸭等；或其它动物，如鱼。

[0399] 在下文论述的以上实施方案的任一个中，使用本发明方法治疗的个体是以下年龄的人类：约一个月至约6个月、约6个月至约1岁、或约1岁至约5岁。在下文论述的以上实施方案的任一个中，使用本发明方法治疗的个体是以下年龄的人类：约5岁至约12岁、约13岁至约18岁、或约18岁至约25岁。在下文论述的以上实施方案的任一个中，使用本发明方法治疗的个体是以下年龄的人类：约25岁至约50岁、约50岁至约75岁、或大于75岁。在下文论述的以上实施方案的任一个中，使用本发明方法治疗的个体是免疫受损的人类。

[0400] 在一些实施方案中，个体患有病毒性疾病或处于患上病毒性疾病的风险中。在一些情况下，所述疾病是选自但不限于由以下组成的组的病毒性疾病：由以下病毒引起的病毒性疾病：寨卡病毒(Zika virus)、乙型肝炎、丙型肝炎、轮状病毒、人免疫缺陷病毒、人嗜T淋巴细胞病毒、DNA病毒(如细小病毒)、腺病毒、乳多空病毒(例如乳头状瘤病毒、多形瘤病毒及SV40)、疱疹病毒(例如I型单纯性疱疹(HSV-I)、II型单纯性疱疹(HSV-II)及埃-巴二氏病毒)、痘病毒(例如痘疮(天花)和牛痘病毒)；及RNA病毒，如逆转录病毒[例如I型人免疫缺陷病毒(HIV-I)、II型人免疫缺陷病毒(HIV-II)、I型人嗜T淋巴细胞病毒(HTLV-I)、II型人嗜T淋巴细胞病毒(HTLV-II)]、正粘病毒(例如流感病毒)、副粘病毒(例如麻疹病毒、腮腺炎病毒、呼吸道合胞病毒)、弹状病毒(例如狂犬病病毒)、仙台病毒(Sendai virus)、小核糖核酸病毒(例如脊髓灰质炎病毒、柯萨奇病毒、鼻病毒)、呼肠孤病毒(例如轮状病毒、科洛拉多蜱传热病毒)、囊膜病毒(例如风疹病毒(风疹)、日本脑炎病毒及塞姆利基森林病毒(Semliki forest virus))、虫媒病毒、杯状病毒(例如戊型肝炎病毒)、黄病毒(例如黄热病病毒、登革热病毒)、冠状病毒、丝状病毒(例如埃博拉病毒和马伯格氏病毒(Ebola and Marburg viruses))以及布尼亚病毒(Bunyaviruses)(例如汉坦病毒、加利福尼亚脑炎病毒

(California encephalitis virus))。

[0401] 在一些实施方案中，个体具有细菌感染或处于患上细菌感染的风险中。在一些实施方案中，个体患有分枝杆菌感染或处于患上分枝杆菌感染的风险中。在一些实施方案中，个体感染有或处于感染了致病细菌的风险中。致病细菌包括例如革兰氏阳性细菌、革兰氏阴性细菌、分枝杆菌等。致病细菌的非限制性实例包括分枝杆菌(例如结核分枝杆菌、鸟分枝杆菌复合体(M.avium complex))、非结核分枝杆菌属、葡萄球菌属、假单胞菌属、沙门氏菌属、奈瑟氏菌属及李斯特氏菌属。在一些情况下，所述细菌为淋病奈瑟氏菌、结核分枝杆菌、麻风分枝杆菌、单核细胞增多性李斯特氏菌、肺炎链球菌、酿脓链球菌、无乳链球菌、绿色链球菌、粪链球菌或牛葡萄球菌。所考虑的致病细菌的其它实例包括但不限于革兰氏阳性细菌(例如李斯特氏菌属、杆菌属如炭疽杆菌、丹毒丝菌属物种)、革兰氏阴性细菌(例如，巴尔通氏体属、布鲁氏杆菌属、弯曲杆菌属、肠杆菌属、埃希氏菌属、弗朗西斯氏菌属、嗜血杆菌属、克雷伯氏菌属、摩根氏菌属、变形杆菌属、普罗维登斯菌属、假单胞菌属、沙门氏菌属、沙雷氏菌属、志贺氏菌属、弧菌属及耶尔森氏菌属物种)、螺旋体细菌(例如，疏螺旋体属物种，包括引起莱姆病的伯氏疏螺旋体)、厌氧细菌(例如，放线菌属和梭菌属物种)、革兰氏阳性和阴性球菌、肠球菌物种、链球菌物种、肺炎球菌物种、葡萄球菌物种、奈瑟氏菌物种。

[0402] 在一些情况下，个体患有或处于患上寄生虫疾病的风险中。可通过本公开方法治疗或预防的寄生虫疾病包括但不限于：阿米巴虫病、疟疾、利什曼虫、球虫病、贾第鞭毛虫病、隐孢子虫病、弓形体病、锥虫病、血吸虫病及丝虫病。

[0403] 在一些情况下，个体患有或处于患上真菌病的风险中。可通过本公开方法治疗或预防的真菌疾病包括但不限于：念珠菌属某些种，包括白色念珠菌；曲霉属某些种；隐球菌属某些种，包括新型隐球菌；芽生菌属某种；肺细胞属某些种；酵母；霉菌或球孢子菌属某些种。

[0404] 在一些情况下，个体患有或处于患上蠕虫感染、吸虫感染等的风险中。还包括各种蠕虫的感染，如但不限于蛔虫病、钩虫病、鞭虫病、类圆线虫病、弓蛔虫病(toxoccariasis)、旋毛虫病、盘尾丝虫病、丝虫病及恶丝虫病。还包括各种吸虫的感染，如但不限于血吸虫病、肺吸虫病及华支睾吸虫病。

[0405] 在一些实施方案中，个体患有自身免疫病症、炎性病症或免疫功能障碍，或处于患上自身免疫病症、炎性病症或免疫功能障碍的风险中。在一些情况下，所述疾病选自但不限于由以下组成的组：过敏、类风湿性关节炎、哮喘、糖尿病、全身性红斑狼疮(SLE)、格雷夫斯氏病、动脉粥样硬化、多发性硬化症、精神分裂症、阿尔茨海默氏病、抑郁症、垂体机能减退、神经变性病症、心血管疾病、肥胖、器官移植、败血症、肝脏疾病、牛皮癣、代谢疾病等。

[0406] 在一些情况下，所述疾病选自由自身免疫疾病和自身免疫相关疾病组成的组，包括但不限于急性播散性脑脊髓炎、急性坏死性出血性脑白质炎、艾迪生氏病、无γ球蛋白血、斑形脱发、淀粉样变性、强直性脊柱炎、抗GBM/抗TBM肾炎、抗磷脂综合征、血管性水肿、再生障碍性贫血、家族性自主神经异常、肝炎、高脂血症、免疫缺陷、内耳疾病、心肌炎、卵巢炎、胰腺炎、视网膜病、血小板减少性紫癜、甲状腺疾病、荨麻疹、轴突和神经元神经病、巴娄病(Balo disease)、白塞氏病、大疱性类天疱疮、心肌病、卡斯尔曼氏病(Castleman disease)、乳糜泻、恰加斯式病(Chagas disease)、慢性疲劳综合征、慢性炎性脱髓鞘多发性神经病、慢性复发性多灶性骨髓炎、丘-施二氏综合征、瘢痕性类天疱疮/良性粘膜炎天疱

疮、克罗恩氏病、柯根综合征(Cogans syndrome)、冷凝集素病、先天性心脏阻滞、柯萨奇心肌炎(Coxsacke myocarditis)、CREST病、原发性混合性冷球蛋白血症、脱髓鞘神经病、疱疹样皮炎、皮肌炎、德维克氏病(Devic's disease)、盘状狼疮、德雷斯勒综合征(Dressler'syndrome)、子宫内膜异位症、嗜酸细胞性食管炎、嗜酸细胞性筋膜炎、结节性红斑、实验性变应性脑脊髓炎、埃文斯综合征(Evans syndrome)、纤维肌痛、纤维性肺泡炎、巨细胞性动脉炎、巨细胞性心肌炎、肾小球性肾炎、古德帕斯彻氏综合征、伴有多血管炎的肉芽肿病、格雷夫斯氏病、格-巴综合征、桥本氏脑炎、桥本氏甲状腺炎、溶血性贫血、亨-舍二氏紫癜(Henoch-Schonlein purpura)、妊娠疱疹、低丙种球蛋白血、特发性血小板减少性紫癜、IgA肾病、IgG4相关的硬化性疾病、免疫调节脂蛋白、包涵体肌炎、间质性膀胱炎、幼年型关节炎、幼年型糖尿病(1型糖尿病)、幼年型肌炎、川崎综合征、兰伯特-伊顿综合征、白细胞分裂性血管炎、扁平苔癣、硬化性苔癣、木样结膜炎、线性IgA病、狼疮、莱姆病、美尼尔氏病(Meniere's disease)、显微镜下多血管炎、混合结缔组织病、莫伦氏溃疡(Mooren'sulcer)、穆-哈二氏病(Mucha-Habermann disease)、多发性硬化症、重症肌无力、肌炎、发作性睡病、视神经脊髓炎、中性白细胞减少、眼部瘢痕的类天疱疮、视神经炎、复发性风湿病、PANDAS、副肿瘤性小脑变性、阵发性睡眠性血红蛋白尿、帕里伯格综合征(Parry Romber syndrome)、帕森尼奇-特纳综合征(Parsonnage-Turner syndrome)、睫状体扁平部炎、天疱疮、周围神经病、静脉周脑脊髓炎、恶性贫血、POEMS综合征、多发性结节性动脉炎、I型、II型和III型自身免疫性多内分泌腺综合征、风湿性多肌痛、多发性肌炎、心肌梗塞后综合症、开胸-心包切开后综合征、黄体酮皮炎、原发性胆汁性肝硬化、原发性硬化性胆管炎、牛皮癣、牛皮癣关节炎、特发性肺纤维化、坏疽性脓皮症、纯红细胞再生障碍、雷诺氏现象(Raynauds phenomenon)、反应性关节炎、反射交感性营养不良、莱特尔氏综合征(Reiter'ssyndrome)、复发性多软骨炎、多动腿综合征、腹膜后纤维化、风湿热、类风湿性关节炎、结节病、施密特综合征(Schmidt syndrome)、巩膜炎、硬皮病、斯耶格伦氏综合征、精子和睾丸自身免疫、僵人综合征、亚急性细菌性心内膜炎、苏萨克氏综合征(Susac's syndrome)、交感性眼炎、高安氏动脉炎(Takayasu's arteritis)、颞动脉炎/巨细胞性动脉炎、血小板减少性紫癜、托-享二氏综合征(Tolosa-Hunt syndrome)、横贯性脊髓炎、1型糖尿病、溃疡性结肠炎、未分化结缔组织病、葡萄膜炎、血管炎、水疱性皮肤病、白斑病及韦格纳氏肉芽肿病。

实施例

[0407] 给出下列实施例,以便为本领域普通技术人员提供有关如何完成和采用本发明的全面公开内容和描述,但不意在对本发明人认为的本发明的范围构成限定,也不意在代表下列实验是全部或仅有的进行的实验。已经努力确保所用数值(例如,量、温度等)的精确性,但是应说明一些实验误差和偏差。除非另外指出,否则份是重量份,分子量是重量平均分子量,温度是摄氏温度,且压力为大气压或接近大气压。可使用标准缩写,例如,bp:碱基对;kb:千碱基;pl:皮升;s或sec:秒;min:分钟;h或hr:小时;aa:氨基酸;kb:千碱基;bp:碱基对;nt:核苷酸;i.m.:肌内(地);i.p.:腹膜内(地);i.n.:鼻内(地);i.v.:静脉内(地);s.c.:皮下(地);M/ml:百万单位或10^6CFU/ml;M:百万单位/小鼠或10^6CFU/小鼠;等等。

[0408] 材料和方法

[0409] 下列材料和方法用于如下所述的实施例中。

[0410] 材料

[0411] RPMI无血清培养基获自Life Technologies(Burlington,Ontario,Canada)。RPMI补充有5-10％胎牛血清、丙酮酸钠、青霉素-链霉素及2-巯基-乙醇以制备完全培养基，其被用于各种细胞培养物中。ConA、PWM及LPS获自Sigma Chemical Company。细胞因子试剂盒和荧光标记的抗小鼠抗体购自eBioscience(San Diego,CA)。抗小鼠FOXP3购自biolegend(San Diego,CA)。Aldra霜剂(5％咪喹莫特)是获自阿尔伯塔大学医院药房(University of Alberta Hospital pharmacy)。使野生型和脂多糖(LPS)阴性新月柄杆菌(LPS^{-ve} CC)在室温下(22-27℃)在孵育箱中生长，并且在4℃或室温下储存在盐水中持续不同的时间段。使野生型弧形柄杆菌(CV)在室温下(22-27℃)在孵育箱中生长，并且在4℃或室温下储存在盐水中持续不同的时间段。

[0412] 方法

[0413] 小鼠

[0414] 6-8周龄C57BL/6或9-11周龄BALB/c雄性或雌性小鼠购自Charles River育种实验室(Charles River Breeding Laboratories)。此项研究中使用的所有动物实验方案都经过阿尔伯塔大学动物护理和使用健康科学委员会(University of Alberta Animal Care and Use Committee for Health Sciences)的批准，并且根据阿尔伯塔大学，埃德蒙顿，加拿大(University of Alberta,Edmonton,Canada)的指南进行。

[0415] 小鼠治疗和样品收集

[0416] 使用如不同实施例和图例中所述的剂量、方案和途径向小鼠单次或多次施用在PBS中的新月柄杆菌(CC)。将所用的CC以两种形式制备:CC-1(在液体PYE培养基中生长且在室温下在盐水中储存的CC)，和CC-2(在液体PYE培养基中生长且在4℃下冰箱中储存的CC)。CC-2在图和描述中也被称为CC。

[0417] 在特定时间下对小鼠施以安乐死之后，收集血液、脾脏、肺脏、肝脏、淋巴结等。使用商用的Vet测试试剂盒(Idexx Laboratories)，用血清样品来测定生化标记。

[0418] 从脾脏分离淋巴细胞

[0419] 在免疫后的特定时间，对小鼠施以安乐死以获得脾细胞。将来自3-5只小鼠的脾脏汇集并且研磨成单细胞悬液，并经由Falcon 100μm尼龙细胞滲滤器过滤。离心以后，将细胞沉淀再悬浮于2ml无菌蒸馏水中并短暂涡旋。立即添加2×PBS并且在短暂涡旋后，用1×PBS使体积变为25ml。对管离心并将细胞沉淀再悬浮于10ml完全RPMI中。将其再次经由Falcon 100μm尼龙细胞滲滤器过滤并离心。将细胞沉淀再悬浮于2ml RPMI培养基中。这些淋巴细胞用于实验。

[0420] 小鼠细胞因子ELISA

[0421] 使用夹心酶联免疫吸附测定(ELISA)试剂盒，按照制造商方案(eBioscience,CA,USA)，就IL-10、GM-CSF、IL-17A、IFN-γ、TNF-α、IL-2、IL-6、IL-1βIL-22、MIP-1α、IL-8/KC的存在对增殖共培养物的上清液或小鼠血清样品中分泌的细胞因子和趋化因子进行测量。1:2至1:50的稀释度用于标准范围在5至2,000pg/ml内的样品。最终，读取ELISA板并且用自动ELISA读板仪(Fluostar Optima,BMG Labtech)计算浓度。

[0422] 抗体应答的评价

[0423] 使用酶联免疫吸附测定(ELISA)测定血清和肺洗出液中的抗体(IgG、IgG2a、IgE)

水平。简言之，将96孔硝化纤维素(Nunc)板用相关抗原(如OVA、MOG肽)包被并在4℃下孵育过夜。将板用含有正常小鼠血清的PBS阻断，接着在室温下用不同稀释度的实验样品孵育2小时。洗涤板4次之后，添加与碱性磷酸酶(AP)缀合的抗小鼠Ig同种型抗体，然后孵育2小时。洗涤板之后，添加PNPP底物并且在405nm波长下在Fluostar ELISA读数器上读取显色。用于抗体检测的所有试剂都获自Southern Biotech(Birmingham,AL)。

[0424] T细胞增殖测定

[0425] 在96孔平底微量滴定板中在一式三份培养物中测量脾T细胞的增殖应答。将来自免疫小鼠的总计4×10^5个脾T细胞和4×10^5个抗原呈递细胞(APC)(来自用18Gy辐照的对照同系基因小鼠的脾细胞)与不同浓度(0.1、1及10μg/mL)的MOG肽混合，在37℃(5%CO_2)下在RPMI培养基(含有10%胎牛血清(FBS))中培养4天。

[0426] 用0.5μCi/孔[^{3}H]-胸苷(Amersham)对细胞进行脉冲12-18h并在滤纸上(Perkin Elmer)采集。在Microbeta Trilux液体闪烁计数器(Perkin Elmer)上对掺入到增殖细胞DNA中的[^{3}H]-胸苷的水平计数。增殖表示为一式三份培养物的平均cpm±SE(标准误差)。

[0427] 表面标记、细胞内IL-10及Foxp3的流式细胞术分析

[0428] 将来自免疫小鼠的总计5×105个细胞进行多色荧光标记的mAb(根据制造商说明书的浓度)的细胞内和细胞外染色。将细胞用Fc小鼠血清(Sigma)孵育以防止非特异性结合并用荧光激活细胞分选仪(FACS)-缓冲液(在1×磷酸盐缓冲盐水(PBS)中的2%胎牛血清)洗涤。在4℃下与用于细胞外标记的抗小鼠CD3e-FITC、CD4-PECy-5、CD25-PE-Cy7、CD8a-APC-Cy7、抗-PD-1-PerCP eFluore 710、抗-CD49b-Alexafluor-700(对于BALB/c和C57bl/6小鼠)等(eBioscience)一起孵育30分钟后，将细胞洗涤两次并固定于固定液(在FACS-缓冲液中的1%多聚甲醛)中5分钟。洗涤两次之后，将细胞与冷的渗透缓冲液(在PBS中的FACS-缓冲液+0.3%皂角苷(Sigma)+5%正常人血清)一起孵育5分钟，然后添加抗小鼠IL-10(eBioscience)和抗Foxp3-PE(biolegend)且在4℃下进一步孵育30分钟。将细胞用含有1%皂角苷的FACS-缓冲液洗涤一次并固定。将其在Fortessa中读取并使用FACS-DIVA软件(Becton Dickinson,Mountain View,CA)分析。基于其相应的同种型-匹配对照单克隆抗体来门控每个标记。

[0429] 人PBMC和DC

[0430] 使用Ficoll-Paque从正常人供体处获得外周血液单核细胞(PBMC)。为了获得树突细胞(DC)，使用在文献中充分确立的程序将粘附的PBMC与重组GM-CSF和IL-4一起在RPMI培养基中培养5-6天。将如个别实施例中所述的与测试材料培养给定时间的人PBMC用针对CD34、CD45、CD11c及CD11b的抗体染色，使用标准程序用商业(eBiosciences)上获得的不同荧光团进行标记。

[0431] 结果

[0432] 以下实施例旨在说明而非限制本发明的范围。

[0433] 将CC的免疫调节作用在如下经由全身和粘膜途径的不同模型和适应症中单独和与不同的抗原一起测试。

[0434] 实施例1:在健康小鼠中经口和鼻内施用CC后在伴刀豆凝集素A(ConA)刺激的脾细胞中新月柄杆菌(CC)对调节炎性细胞因子的作用

[0435] 将C57/b16雄性小鼠用CC以500x106CFU/小鼠或PBS对照每周两次经口或鼻内治疗

五次。在最后一次治疗后8天对小鼠施以安乐死。分离脾脏并用T细胞促分裂素ConA以1ug/ml浓度离体刺激24小时。收集上清液并且使用ELISA测量细胞因子(IFN-γ、TNF-α、IL-6及IL-17A)(图1)。这些结果表明,CC的治疗在用Con A离体刺激后的脾细胞中下调炎性细胞因子的产生,并且提示CC在抑制来自包括病毒、细菌、真菌的多种感染以及来自环境毒素、药物反应和自身免疫病症的由T细胞介导的炎症方面的作用。

[0436] 实施例2:在健康小鼠中经口和鼻内施用CC后新月柄杆菌(CC)调节来自美洲商陆(PWM)刺激的脾细胞的炎性细胞因子的作用

[0437] 将C57/b16雄性小鼠用CC以500x106CFU/小鼠或PBS对照每周两次经口或鼻内治疗五次。在最后一次治疗后8天对小鼠施以安乐死。分离经治疗的小鼠的脾脏并用B细胞促分裂素PWM以0.1ug/ml浓度离体刺激24小时。收集上清液以便使用ELISA进行细胞因子(IFN-γ、TNF-α、IL-6及IL-17A)测量(图2)。这些结果表明,CC的治疗下调在用PWM离体刺激后的脾细胞中炎性细胞因子的产生,并且提示CC减轻在感染和非感染相关的全身炎性病症中的促炎性细胞因子的过度产生方面的作用。

[0438] 实施例3:在经口和鼻内施用后新月柄杆菌(CC)对抗炎细胞因子IL-10的体内诱导的作用:

[0439] 将五只C57/b16雄性小鼠组用CC以500x10^6CFU/小鼠或PBS对照每周两次经口或鼻内治疗五次。在最后一次治疗后8天对小鼠施以安乐死并且分离脾脏。将脾细胞用培养基、ConA及PWM培养24小时。收集上清液以便使用ELISA进行IL-10测量(图3A-图3C)。所获结果显示在有或没有刺激剂下24小时培养后CC上调脾细胞中离体IL-10的产生并且提示CC可诱导体内IL-10产生。这些结果还表明CC在炎性病状中重建体内平衡方面的全身免疫调节和抗炎作用。

[0440] 总之,图1、图2和图3中所示的结果提示CC具有诱导较高水平的抗炎细胞因子IL-10和下调炎性细胞因子IFN-γ、TNF-α、IL-6及IL-17A的水平的能力。促炎性细胞因子在许多疾病的发病机制中发挥重要作用且因此人们对开发在一系列罹患的疾病中调节它们的过度产生的治疗剂感兴趣。

[0441] 实施例4:新月柄杆菌(CC)对从CC治疗的小鼠中分离的离体LPS刺激的脾细胞的IL-10产生的作用:

[0442] 将雌性C57/b16小鼠用CC以500x10^6CFU/小鼠或PBS对照每周两次经由管饲法经口治疗四次。在最后一次治疗后4天对小鼠施以安乐死并且收集脾脏。用LPS以1ug/ml浓度刺激脾细胞24和72小时。收集上清液并使用ELISA测量IL-10(图4)。所获结果显示与安慰剂组(PBS)相比,CC在LPS刺激后上调脾细胞中的离体IL-10产生。这些研究提示CC在正常化促炎性细胞因子的失调释放方面的抗炎活性及对炎性应答和/或自身免疫病症的保护。

[0443] 实施例5:在经口治疗后新月柄杆菌(CC)对肠相关肠系膜淋巴结中的促炎性细胞因子的作用:

[0444] 为了确定CC对肠淋巴组织中炎性细胞因子水平的作用,将雌性C57/b16小鼠用CC以500x10^6CFU/小鼠或PBS对照每周两次经口治疗四次。在最后一次治疗后三天,对小鼠施以安乐死并收集局部肠系膜淋巴结。在24小时LPS刺激后收集的上清液中测定细胞因子水平。CC的经口施用与PBS组相比造成IFN-γ、IL-6及IL-17A的水平下降(图5)。这些结果显示CC可下调局部肠系膜淋巴结中的Th1和Th17细胞因子的产生。因此,CC具有降低多种炎性病

症中的TH1和/或TH17介导的促炎性细胞因子水平的能力，其中免疫失调和炎症是由以下外部或内部刺激或微生物触发：诸如革兰氏阳性和革兰氏阴性细菌、病毒、真菌、寄生虫、LPS、毒素、自身抗原、糖基磷脂酰肌醇、组织损伤(外伤、烧伤)等。

[0445] 实施例6：新月柄杆菌(CC)在经口治疗后的小鼠中全身免疫调节的作用：

[0446] 将雌性C57/b16小鼠用CC以500x10^{6}CFU/小鼠或PBS对照每周两次经口治疗四次。在最后一次治疗后4天对小鼠施以安乐死并且收集脾脏。通过流式细胞术分析表达IL-10+的CD3+CD4+和CD3+CD8+细胞的百分比。CC的治疗造成脾细胞中CD4+和CD8+T细胞上的细胞内IL-10的表达增加(图6)。总的来说，图4-图6中示出的结果显示CC在炎性和自身免疫病症中具有局部和全身正常化免疫失调的强能力。

[0447] 实施例7：在皮下治疗后新月柄杆菌(CC)对调节脾脏中的促炎性细胞因子产生的作用：

[0448] 向三只C57/b16雄性小鼠组每周一次经由皮下途径施用CC(500x10^{6}CFU/小鼠)或PBS持续四周。在最后一次治疗后28天对小鼠施以安乐死。采集脾脏并且将脾细胞用ConA培养。在24小时ConA刺激后收集的上清液中测定细胞因子水平。图7中所示的结果表明CC导致持续调节IFN-γ、TNF-α及IL-6细胞因子的产生(图7)。因此，CC可甚至在疗法停止之后还提供持久的免疫调节作用。

[0449] 实施例8：在用新月柄杆菌(CC)经口治疗之后先天性和适应性免疫细胞的调节：

[0450] 将三只C57/b16雄性小鼠组每周一次用CC(500x10^{6}CFU/小鼠)或PBS经口治疗持续四周。在最后一次治疗后28天对小鼠施以安乐死并且采集脾细胞并通过流式细胞术来分析。CC的经口治疗造成CD8$^+$、CD8$^+$CD25$^+$及NKT(CD3$^+$CD49b$^+$)细胞上的FOXP3表达增加和NK细胞上的PD-1表达增加(图8)。因此，CC诱导各种调控性淋巴细胞来控制炎症。这些数据表明CC可通过调控先天性和适应性免疫细胞上的不同调控性分子的表达来诱导体内平衡，且因此CC可用于控制各种疾病中的过度炎症。已显示NK细胞上的PD-1表达控制分枝杆菌感染中的炎性应答。另外，还显示NK上的PD-1保护免受包括病毒性、细菌性及自身免疫病症。

[0451] 已显示NK和/或NKT细胞下调包括以下的若干疾病中的自身免疫应答：多发性硬化症、类风湿性关节炎、全身性红斑狼疮、斯耶格伦氏综合征、自身免疫性甲状腺病、牛皮癣、白塞氏病、I型糖尿病、神经变性疾病等。因此，本公开提出用于预防和/或治疗一系列炎性、过敏性及自身免疫病症的有吸引力的生物治疗剂。因此，本公开总体上提出一种通过调节适应性和先天性T和/或NK和/或NKT细胞的活性来预防和/或治疗感染性和非感染性情形下的全身和局部炎症的策略。

[0452] 实施例9：在用新月柄杆菌(CC)皮下治疗之后脾细胞中的T细胞的调节：

[0453] 将三只C57/b16雄性小鼠组每周一次用CC(500x10^{6}CFU/小鼠)或PBS皮下治疗四周。在最后一次治疗后28天对小鼠施以安乐死并且采集脾细胞并通过流式细胞术来分析。CC的皮下治疗造成CD4+、CD4$^+$CD25$^+$、CD8$^+$及CD8$^+$CD25$^+$T细胞上的FOXP3表达增加(图9)。因此，CC的胃肠外施用也可提供持久的免疫调节作用。这些结果显示CC在诱导和扩增调控性T细胞亚组中的作用。已显示T调控性细胞在包括以下的广泛范围疾病中抑制炎性活性：自身免疫性脑脊髓炎、IBD、细菌诱导的结肠炎、1型糖尿病、嗜酸细胞性气道炎症、移植物抗宿主疾病、器官移植等。

[0454] 实施例10：新月柄杆菌(CC)在败血症/炎症的LPS激发模型中控制全身炎症方面展

现积极益处:调节血清中的细胞因子水平。

[0455] 用LPS在100μl PBS中以7mg/Kg腹膜内激发3只C57/bl6雄性小鼠组,并且在用LPS体内激发2小时和24小时后用CC(500x10^6CFU/小鼠)经口治疗。健康未激发的和饲喂PBS的小鼠也被纳入作为对照。在第二治疗之后对小鼠施以安乐死并且收集血液样品并通过ELISA分析其中的细胞因子。LPS激发的小鼠在血清中具有高水平的炎性细胞因子。相比之下,CC治疗下调炎性细胞因子IL-1β和IL-6的产生并上调抗炎细胞因子IL-10的产生(图10)。因此,CC促进非损伤性免疫应答。IL-1β和IL-6的诱导与许多急性和慢性炎性疾病及自身免疫疾病有关,如败血症、MS、阿尔茨海默氏病、帕金森氏病、RA、痛风、代谢疾病(动脉粥样硬化、II型糖尿病)、高血压、慢性阻塞性肺病(COPD)、哮喘、牛皮癣及过敏。因此,CC可有助于管理和改善这些炎性医学病状。

[0456] 实施例11:新月柄杆菌(CC)在败血症/炎症模型中控制局部炎症方面展现积极益处:调节肺脏和肝脏中的细胞因子水平。

[0457] 用LPS在100μl PBS中以7mg/Kg腹膜内激发3只C57/bl6雄性小鼠组,并在用LPS体内激发2小时和24小时后用CC(500x106CFU/小鼠)经口治疗。健康未激发的和饲喂PBS的小鼠也被纳入作为对照。在这些研究中,将所用的CC以两种形式制备:CC-1(在液体PYE培养基中生长且在室温下在盐水中储存的CC),和CC-2(在液体PYE培养基中生长且在4℃下冰箱中储存的CC)。在CC-1和CC-2的第二次治疗之后对小鼠施以安乐死,并且采集肺脏和肝脏,然后测定其匀浆中的细胞因子。与LPS激发组相比,CC-1和CC-2都下调肺脏和肝脏中炎性细胞因子TNF-α、IL-6、IL-1β及IL-17A的产生(图11)。这些结果表明CC可用于控制炎性过程并正常化组织功能,包括与以下有关的炎症后的医学病状:在各种(肠、肺、肝、脑、皮肤、心脏等)器官中的病毒和细菌病原体、组织损伤、细胞应激、代谢扰动等。LPS介导的败血症是急救护理、手术及烧伤病房中死亡的常见原因。通过靶向宿主免疫组分而致力于改善LPS介导的致死性炎性级联的治疗方法可具有临床和治疗优势。

[0458] 实施例12:新月柄杆菌(CC)在LPS激发的小鼠炎症模型中对肝损伤的生化参数展现积极效果:

[0459] 用LPS在100μl PBS中以7mg/Kg腹膜内激发3只C57/bl6雄性小鼠组,并在用LPS体内激发2小时和24小时后用CC(500x10^6CFU/小鼠)经口治疗。健康未激发的和饲喂PBS的小鼠也被纳入作为对照。在这些研究中,将所用的CC以两种形式制备:CC-1(在液体PYE培养基中生长且在室温下在盐水中储存的CC),和CC-2(在液体PYE培养基中生长且在4℃下冰箱中储存的CC)。在CC-1和CC-2的第二次治疗之后对小鼠施以安乐死,并采集血液样品以确定对生化标记的作用。CC-1和CC-2的治疗都能使LPS激发的小鼠的葡萄糖(GLU)、球蛋白(GLOB)、丙氨酸转氨酶(ALT)、总磷酸盐(TP)及总胆红素(TBIL)水平正常化至非激发的且饲喂PBS的小鼠的水平(图12)。这些结果表明CC可有效地用于治疗各种炎症介导的病症,包括肝相关疾病。

[0460] 实施例13:新月柄杆菌(CC)预防LPS激发的小鼠模型中的肝损伤:

[0461] 用LPS在100μl PBS中以7mg/Kg腹膜内激发3只C57/bl6雄性小鼠组,并在用LPS体内激发2小时和24小时后用CC(500x10^6CFU/小鼠)经口治疗。健康未激发的和饲喂PBS的小鼠也被纳入作为对照。在这些研究中,将所用的CC以两种形式制备:CC-1(在液体PYE培养基中生长且在室温下在盐水中储存的CC),和CC-2(在液体PYE培养基中生长且在4℃下冰箱中

储存的CC)。在CC-1和CC-2的第二次治疗之后对小鼠施以安乐死,并收集各种器官。在CC-1和CC-2两者的情况下都未观察到肺、肝及其它器官的炎症或损伤。进行肝切片的H&E染色。图13中所示的结果显示与LPS激发的小鼠相比,通过经口途径施用的CC在预防LPS诱导的炎症及肝损伤中的保护作用。肝脏的大规模破坏与许多医学病状有关,这些医学病状是由归因于感染性和非感染性发病机制的不希望的炎性活性造成。因此,CC在预防和改善由自身免疫性肝炎、酒精相关性肝病、病毒介导的肝炎等所致的肝损伤中具有强大潜力。

[0462] 实施例14:在用新月柄杆菌(CC)经口治疗后咪喹莫特(IMQ)诱导的牛皮癣样皮炎小鼠模型中细胞因子的调节:

[0463] 向10-11周龄Balb/c雌性小鼠在剃过毛的背部施用局部剂量的6.25mg 5%IMQ霜剂(Aldra,咪喹莫特)持续连续6天。从第3天起(5天一周,持续两周),用CC以500x10^6CFU/小鼠经口治疗小鼠。在最后一次治疗后3天对小鼠施以安乐死并采集脾脏。将脾细胞用培养基离体培养4天并且检查培养上清液中的细胞因子(图14)。与PBS治疗的牛皮癣小鼠相比,CC的治疗造成Aldra诱导的牛皮癣小鼠中IFN-γ、IL-6、IL-17A及IL-22的产生减少(图14)。这些研究表明CC可纠正炎性疾病和自身免疫疾病中的细胞因子失调并产生有益的治疗效果。除牛皮癣之外,免疫细胞在真皮和表皮中的浸润也发生在其它慢性皮肤疾病如特应性皮炎、反常性痤疮、红斑痤疮等中。因此,CC可用于治疗具有炎性组分的各种皮肤病症。总之,图14中所示的结果表明CC具有全身免疫调节和抗炎活性以便保护免于病原体或自身免疫相关的炎性应答。

[0464] 实施例15:新月柄杆菌(CC)在罹患DSS诱导的炎性肠病(IBD)的小鼠的结肠组织中对减少促炎性细胞因子和趋化因子的作用。

[0465] 向5只雄性C57bl/6组给予饮用水中的3%葡聚糖硫酸钠(DSS)持续连续7天。在DSS开始的同一天用CC(500x10^6CFU/小鼠)治疗小鼠。水治疗的小鼠用作对照。在第10天,对小鼠施以安乐死并且采集结肠组织并且培养24h。使用ELISA测定培养上清液中的细胞因子。所获结果表明CC减少促炎性细胞因子IFN-γ、TNF-α、IL-1β、及趋化因子IL-8/KC和MIP-1α(图15)。因此,CC的经口治疗在鼠DSS诱导的结肠炎模型(对于IBD)中降低局部结肠中炎性细胞因子和趋化因子的异常水平,这解释了级联的激活在IBD中导致上皮通透性、细胞凋亡、溃疡、腹泻等。

[0466] 实施例16:新月柄杆菌(CC)在实验性自身免疫性脑脊髓炎(EAE)模型中对抑制自身抗原特异性T细胞和抗体应答的作用。

[0467] 为了确定CC在减轻自身抗原特异性免疫应答中的作用,将五只C57B16雌性小鼠组用在CFA中乳化的200μg MOG_{35-55}肽在100μl盐水中皮下免疫。另外,在第0天和第3天,小鼠腹膜内接受400ng在200μl盐水中的百日咳毒素。从免疫的第3天开始,将小鼠每三天连续地用CC(500x10^6cfu/小鼠)经口治疗直到实验结束。PBS治疗的激发小鼠被用作对照。在免疫后30天对小鼠施以安乐死并收集脾脏和血液样品。在脾细胞中检查针对MOG肽(10、1及0.1μg/ml)的T细胞应答。通过ELISA分析血清样品中的抗MOG抗体(IgG和IgG2a)滴度。有趣的是,与PBS对照组相比,CC减轻自身抗原MOG特异性T细胞应答(图16)。与PBS对照组相比,CC还降低自身抗原MOG特异性IgG和IgG2a抗体滴度(图16)。这些结果提示CC可降低自身抗原特异性T和B细胞应答。EAE模型是人类炎性脱髓鞘疾病,多发性硬化症(MS)的常用模型。MS是中枢神经系统(CNS)的炎性疾病。EAE是一种复杂病状,其中免疫病理与神经病理机制之间的相互

作用产生MS的病理特征，即炎症、脱髓鞘、轴突缺失及神经胶质增生。因此，CC可有效治疗自身免疫和神经障碍、自身免疫性血液疾病、自身免疫性溶血性贫血等。

[0468] 实施例17：新月柄杆菌(CC)在卵清蛋白诱导的小鼠气道炎症模型中对减轻过敏原(OVA)特异性抗体和细胞因子应答的作用。

[0469] 为了确定CC在气道/肺炎性疾病中的作用，在第1天和第6天，用在400μl盐水中的10μg卵清蛋白和2mg Al(OH)$_3$腹膜内敏化5只Balb/c雄性小鼠组。在第12天和第14天用50μg卵清蛋白鼻内激发(15μl/鼻孔)小鼠。从敏化的第7天开始，每三天用CC(500x10^{6}CFU/小鼠)经口治疗小鼠直到第17天。在单独的组中，将小鼠在第13天用地塞米松(DEX，2mg/Kg，i.p.)单独治疗一次或用地塞米松和CC治疗。对照小鼠以与CC相同的方案接受盐水。在最后一次治疗的次日对小鼠施以安乐死，收集血液样品、肺洗出液和脾脏。将脾细胞的单细胞悬液(2x10^{6}个细胞/ml)用50μg OVA培养96h并且通过ELISA分析培养上清液中的细胞因子(IL-4和IL-6)水平。CC的经口治疗减少OVA敏化小鼠中OVA特异性IgE在血清和肺洗出液中的产生(图17)。发现通过CC治疗，脾脏中的IL-4和IL-6水平也降低(图18)。与地塞米松单独治疗相比，CC治疗与地塞米松的组合进一步造成脾脏中的IL-4和IL-6水平进一步降低(图19)。这些数据提示CC的治疗预防小鼠中OVA诱导的过敏性气道炎症。过敏是一种复杂疾病，其中多种免疫细胞和炎性介质促进过敏性疾病的起始和表现。过敏是IgE介导的超敏反应的最常见结果。IL-4和IL-6产生的增加与过敏性疾病有关。IgE在血清中的存在是由B细胞中IL-4介导的Ig类别转换驱动的过敏性疾病的标志。IgE依赖性过敏反应可影响一种或多种靶器官及过敏性疾病，如鼻炎、鼻窦炎、结膜炎、哮喘、皮炎和食物过敏等。

[0470] 实施例18：新月柄杆菌(CC)在高脂饮食诱导的肥胖模型中治疗代谢病症和减轻全身性炎症的作用。

[0471] 向五只C57bl/6小鼠组饲喂高脂饮食持续4-6个月并且每周三次用CC(500x10^{6}cfu/小鼠)治疗4-6个月。PBS治疗的高脂饮食饲喂的小鼠用作对照。在约第180天，终止实验之前进行葡萄糖耐受性试验。使用OneTouch监测系统测量血糖。对小鼠施以安乐死并收集血液、肝脏和脾脏。血清样品用于通过兽医测试(Vet test)来测定生化参数。制备肝脏匀浆并且通过ELISA测定促炎性细胞因子(IFN-γ、TNF-α、IL-6、IL-1β)。将脾细胞(2x10^{6}个细胞/ml)用LPS(1mg/ml)培养24h并且通过ELISA分析培养上清液中的细胞因子(IFN-γ、TNF-α、IL-6)。与高脂饮食对照小鼠相比，CC的经口治疗显著减少肝脏(图20)和脾脏(图21)中的促炎性细胞因子，提示CC可有效地减轻慢性和全身性炎症。在高脂饮食诱导的肥胖模型中，CC的经口治疗还在与代谢疾病有关的生化参数中提供积极益处(图22)。此外，进行CC治疗的小鼠显示与对照组相比改善的葡萄糖耐受性(图23)。已充分确定，肥胖与低度炎症有关，低度炎症又促成以下许多代谢病症，包括2型糖尿病、心血管疾病、高血压、高胆固醇血症、高甘油三酯血症、非酒精性脂肪肝疾病、脱发等。在肥胖状态下，许多炎性细胞因子和趋化因子(例如，IFN-γ、TNF-α、IL-6、IL-1β等)的产生是失调的。肥胖也与造成葡萄糖耐受不良的胰岛素抗性和非酒精性脂肪肝疾病有关。已显示TNF-α活性的抑制还显著抑制脂肪性肝炎在饲喂酒精的动物中的发展。高胆固醇与冠心病(动脉粥样硬化)、中风、外周血管疾病、糖尿病及高血压的风险升高有关。升高水平的甘油三酯与动脉粥样硬化有关并且还增加急性胰腺炎的风险。当肾脏不能有效地消除尿酸时，出现高尿酸水平。可引起高尿酸的其它因素包括肥胖、甲状腺机能减退等。尿酸的积聚可造成炎症及痛风发作的剧烈

疼痛。肌酸激酶水平升高见于心脏病发作、所有类型的肌营养不良、内分泌病症、神经肌肉疾病等中。已知促炎性细胞因子如TNF-α、IL-6、IFN-γ、IL-1β参与了肥胖、肥胖相关病状如2型糖尿病、胰岛素抗性、非酒精性脂肪肝疾病、酒精诱导的肝脏疾病、血管功能障碍相关的神经变性过程如阿尔茨海默病、神经精神病症如抑郁症、精神分裂症等。线粒体活性氧物质(ROS)驱使慢性人类疾病中促炎性细胞因子(TNF-α、IL-6、IFN-γ、IL-1β)产生。这些研究显示CC的治疗在高脂饮食的肥胖小鼠中减少与代谢病症有关的血清生化标记、改善葡萄糖耐受性并减少肝脏中的促炎性细胞因子。

[0472] 实施例19:新月柄杆菌(CC)在携带EL-4淋巴瘤的小鼠中降低与抗癌药物环磷酰胺有关的肝和肾毒性的作用。

[0473] 为了确定CC在降低与治疗性治疗有关的毒性中的作用,将五只C57B16小鼠组用在100μl盐水中的0.25x10^6个EL-4细胞/小鼠在左下胁腹中皮下激发。从用EL-4细胞激发后第5天开始,每周一次经口施用CC(50x10^6cfu/小鼠)。在第17天和第21天,将小鼠用环磷酰胺以150mg/Kg腹膜内治疗。健康的未激发的及环磷酰胺单独治疗的激发的小鼠被用作对照。在EL-4激发后第30天对小鼠人道地施以安乐死并且收集血液样品。CC连同环磷酰胺的治疗在携带EL-4肿瘤的小鼠中将磷酸盐(PHOS)和总胆红素(TBIL)的血清水平正常化至非激发的正常小鼠的水平(图24)。这些结果表明CC可用于有效地降低抗癌剂或治疗性治疗的毒性。

[0474] 实施例20:新月柄杆菌(CC)在B16转移性癌症模型中降低与抗癌药物有关的器官毒性的作用。

[0475] 为了确定CC在降低与癌症化疗有关的毒性中的作用,将五只C57B16小鼠组用在100μl盐水中的0.4x10^6个B16细胞/小鼠腹膜内激发。在B16激发后第7天和第10天将小鼠用顺铂(4mg/kg)腹膜内治疗并且每周一次经口施用CC(50x10^6cfu/小鼠)。健康的未激发的及顺铂单独治疗的激发的小鼠被用作对照。在B16激发后第30天对小鼠施以安乐死并且收集血液样品以确定对血清生化标记的作用。CC连同顺铂的治疗在携带B16转移性癌症的小鼠中将磷酸盐(PHOS)、尿素、总胆红素(TBIL)及天冬氨酸转氨酶(AST)的血清水平正常化至非激发的正常小鼠的水平(图25)。这些结果表明CC可用于有效地降低抗癌剂或治疗性治疗的毒性。

[0476] 实施例21:新月柄杆菌(CC)在B16黑色素瘤小鼠模型中降低升高的与检查点抑制剂抗体(抗PD-1)有关的肝毒性的生化参数水平的作用。

[0477] 为了确定CC在降低与治疗性抗体有关的毒性中的作用,将五只C57B16小鼠组用在100μl盐水中的0.4x10^6个B16细胞/小鼠在左下胁腹中皮下激发。从用B16黑色素瘤癌细胞激发后第3天开始,每周一次经口施用CC(50x10^6cfu/小鼠)。在用CC第一次治疗之后两天,腹膜内施用抗PD-1抗体(200ug/小鼠)并且每3-4天继续进行。健康的未激发的及抗PD-1抗体单独治疗的激发的小鼠被用作对照。在肿瘤激发后第25天对小鼠施以安乐死并且收集血液样品以确定对生化标记的作用。CC连同抗PD-1单克隆抗体的治疗在携带B16肿瘤的小鼠中将磷酸丙氨酸转氨酶(ALT)和天冬氨酸转氨酶(AST)的血清水平正常化至非激发的正常小鼠的水平(图26)。这些结果表明CC可用于有效地降低治疗性和检查点抑制剂抗体或治疗性治疗的毒性。

[0478] 实施例22:LPS阴性新月柄杆菌(LPS-^{ve} CC)在败血症/炎症的LPS激发模型中保护

小鼠免受肝损伤:调节肝脏中的细胞因子水平。

[0479] 为了确定脂多糖阴性(LPS-ve)CC在免疫调节中的作用,将C57/b16雌性小鼠用在200μl盐水中的LPS以25mg/Kg腹膜内激发并且在用LPS体内激发2h和20h后用LPS-ve CC(500x10^{6}CFU/小鼠)经口治疗。健康未激发的和饲喂PBS的小鼠也被纳入作为对照。在第二次治疗24h之后对小鼠施以安乐死,并且采集肝脏,然后测定其匀浆中的细胞因子。LPS激发的小鼠在肝脏匀浆中具有高水平的炎性细胞因子和趋化因子。相比之下,LPS-ve CC治疗下调炎性细胞因子IFN-γ、TNF-α、IL-1β、IL-6、IL-8/KC及趋化因子MIP-1α的产生并上调抗炎细胞因子IL-10的产生(图27)。这些结果表明类似于使用野生型CC所获得的结果,LPS-ve CC在控制炎性过程中也展现积极的效果。因此,LPS阴性CC可用于控制炎性过程并正常化组织功能,包括炎症后的医学病状。

[0480] 实施例23:弧形柄杆菌(CV)在人PBMC中减少由益生菌或致病细菌诱导的促炎性细胞因子的作用。

[0481] 将人PBMC(4x10^6/孔)用灭活的鼠李糖乳杆菌(LB)或单核细胞增多性李斯特氏菌(LM)(50x10^{6}CFU/ml)刺激6h。然后添加CV(250x10^{6}CFU/ml)并且再孵育板24h或96h。收集培养上清液并且通过ELISA测定IFN-γ和TNF-α。CV的治疗降低由LB和LM诱导的IFN-γ和TNF-α的水平(图28)。这些结果提示柄杆菌属的其它物种可减轻与细菌或病毒病原体有关的炎症。这些结果还提示柄杆菌属物种可用于治疗由微生物组相关和不相关的微生物诱导的不希望的炎性应答。此外,它们可用于调节微生物组治疗剂的免疫调节活性。

[0482] 实施例24:新月柄杆菌(CC)在离体操纵人髓样树突细胞中的作用。

[0483] 将从外周血液单核细胞分化来的人髓样树突细胞(2x10^6/ml)在CC(50或10CFU/ml)的不存在和存在下培养24h。收集培养上清液并且通过ELISA检查IL-10水平。所获结果提示CC可生成产生IL-10的调节的DC群(图29)。树突细胞(DC)是适应性免疫的关键调节物,其具有诱导T细胞抑制和耐受性的潜力。由DC产生的IL-10在调控性T细胞的生成、扩增和维持中发挥作用。这些结果提示CC可用于离体操纵DC以用于基于DC的免疫治疗策略。

[0484] 实施例25:新月柄杆菌(CC)对多能干细胞从人PBMC分化/扩增为髓性细胞的作用。

[0485] 将人PBMC(4x10^6/孔)与CC(500x10^6、50x10^6、10x10^{6}及1x10^{6}CFU/ml)和盐水一起培养10天。针对表面标记CD34、CD45、CD11c及CD11b对PBMC进行染色。针对CD34+CD45-多能干细胞来门控细胞,由此进一步针对CD11c+和CD11b+DC和巨噬细胞进行门控,并且通过流式细胞术分析数据。所获结果提示CC可将干细胞分化为髓性细胞(图30)。髓性细胞来源于多能造血干细胞。这些细胞在先天性和适应性免疫、炎性反应、免疫体内平衡的恢复、骨重建等中发挥关键作用。因此,CC可导致髓性细胞由干细胞的分化和/或扩增以用于患者特异性免疫疗法中。

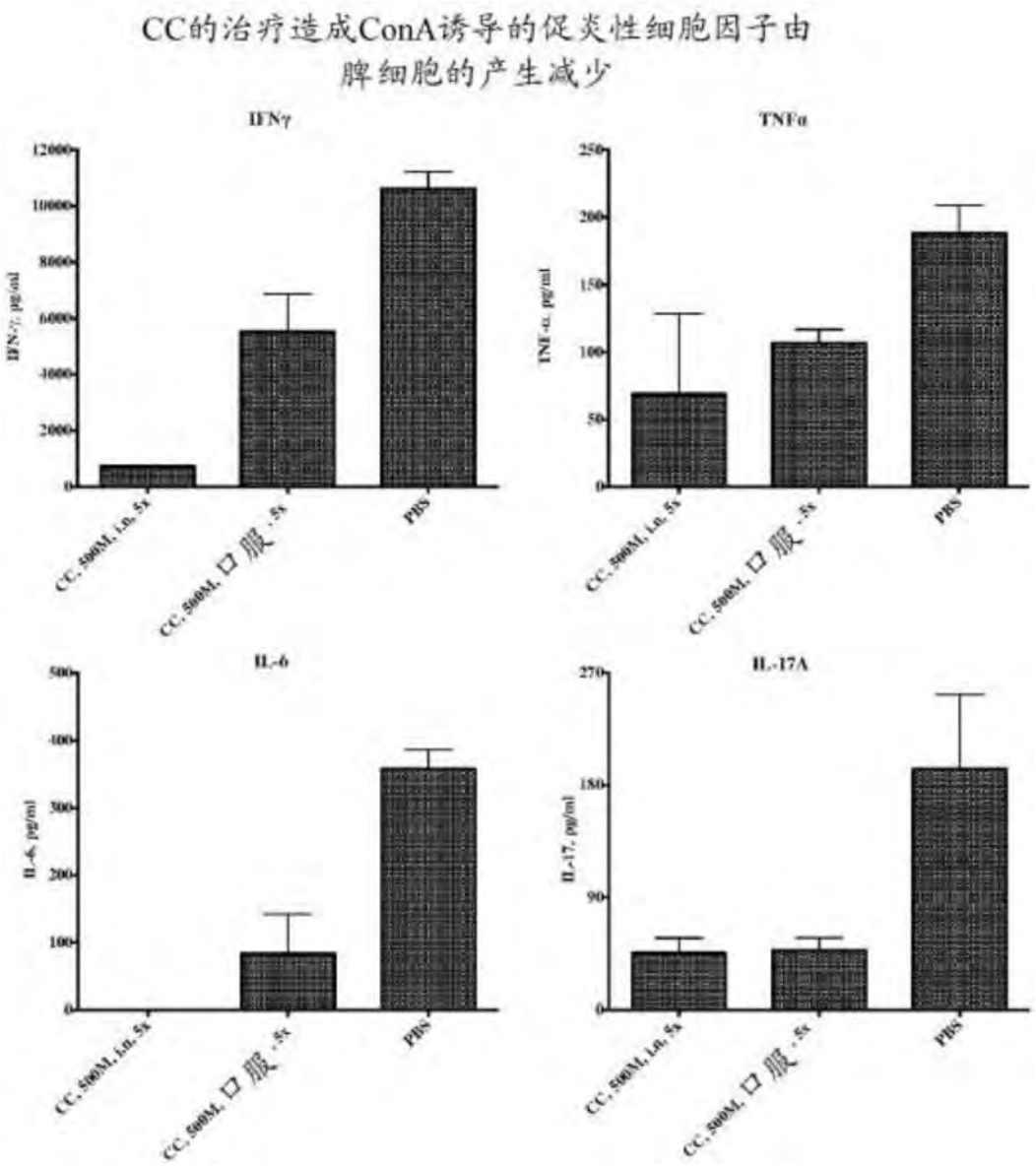

CC的治疗造成ConA诱导的促炎性细胞因子由
脾细胞的产生减少
IFNγ
IFN-γ, pg/ml
12000
10000
8000
6000
4000
2000
0
CC, 500M, i.o, 5x
CC, 500M, 口服, 5x
PBS
TNFα
TNF-α, pg/ml
250
200
150
100
50
0
CC, 500M, i.o, 5x
CC, 500M, 口服, 5x
PBS
IL-6
IL-6, pg/ml
500
400
300
200
100
0
CC, 500M, i.o, 5x
CC, 500M, 口服, 5x
PBS
IL-17A
IL-17, pg/ml
270
180
90
0
CC, 500M, i.o, 5x
CC, 500M, 口服, 5x
PBS

图1

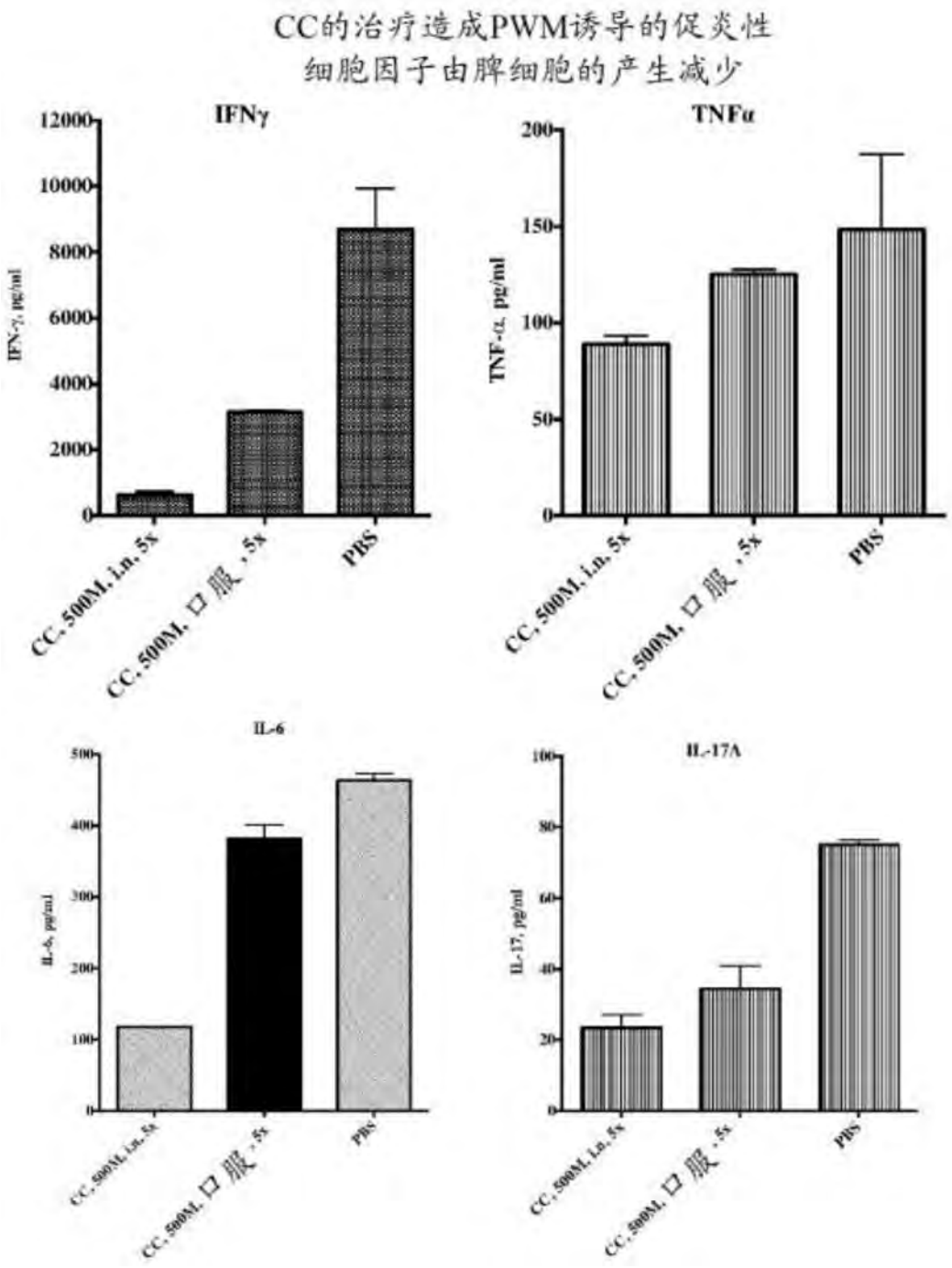

CC的治疗造成PWM诱导的促炎性
细胞因子由脾细胞的产生减少
IFNγ
IFN-γ, pg/ml
12000
10000
8000
6000
4000
2000
0
CC, 500M, i.n, 5x
CC, 500M, 口服, 5x
PBS
TNFα
TNF-α, pg/ml
200
150
100
50
0
CC, 500M, i.n, 5x
CC, 500M, 口服, 5x
PBS
IL-6
IL-6, pg/ml
500
400
300
200
100
0
CC, 500M, i.n, 5x
CC, 500M, 口服, 5x
PBS
IL-17A
IL-17, pg/ml
100
80
60
40
20
0
CC, 500M, i.n, 5x
CC, 500M, 口服, 5x
PBS

图2

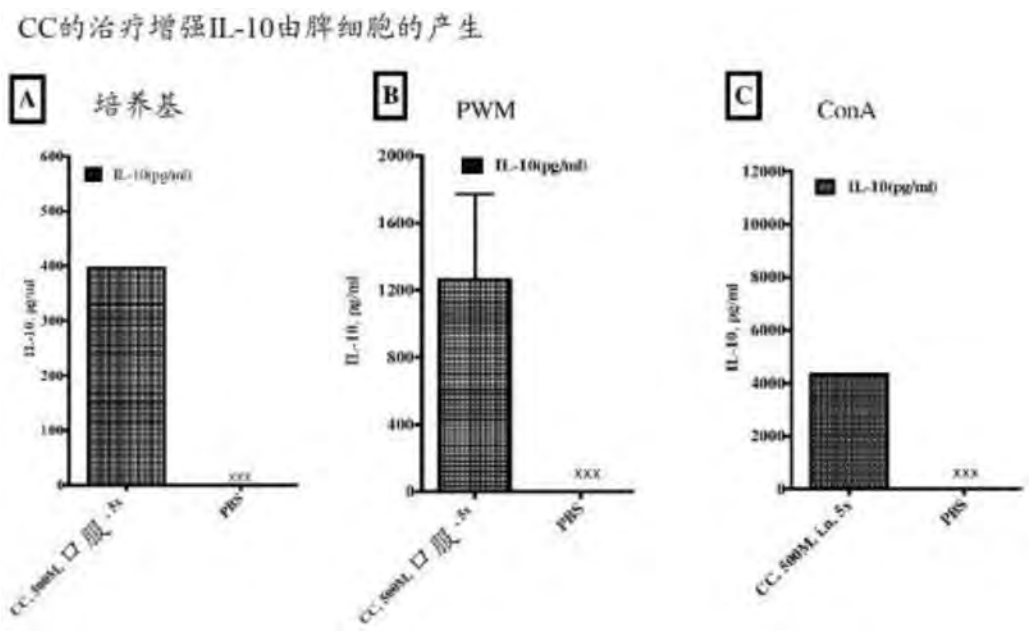

CC的治疗增强IL-10由脾细胞的产生
A
培养基
B
PWM
C
ConA
IL-10(pg/ml)
IL-10, pg/ml
xxx
PBS

图3

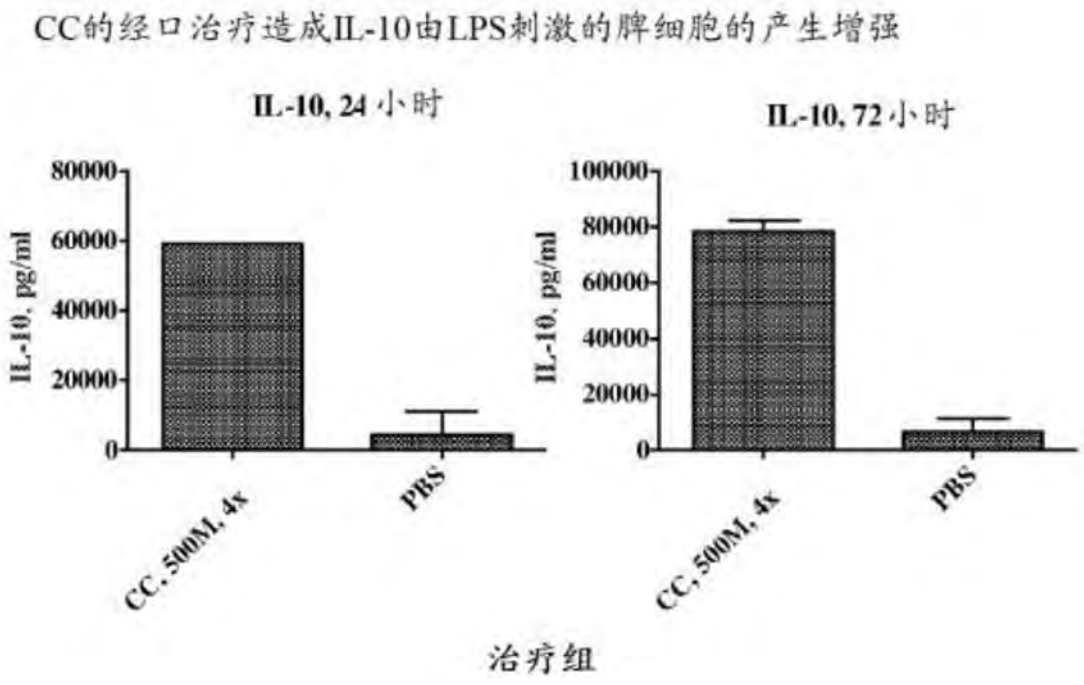

CC的经口治疗造成IL-10由LPS刺激的脾细胞的产生增强
IL-10, 24 小时
IL-10, 72 小时
IL-10, pg/ml
CC, 500M, 4x
PBS
治疗组

图4

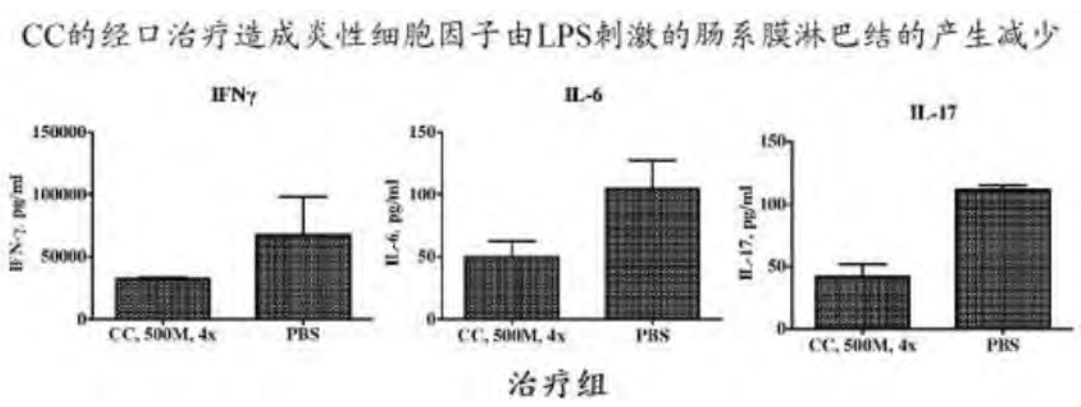

CC的经口治疗造成炎性细胞因子由LPS刺激的肠系膜淋巴结的产生减少
IFNγ
IL-6
IL-17
IFN-γ, pg/ml
IL-6, pg/ml
IL-17, pg/ml
150000
100000
50000
0
150
100
50
0
CC, 500M, 4x
PBS
治疗组

图5

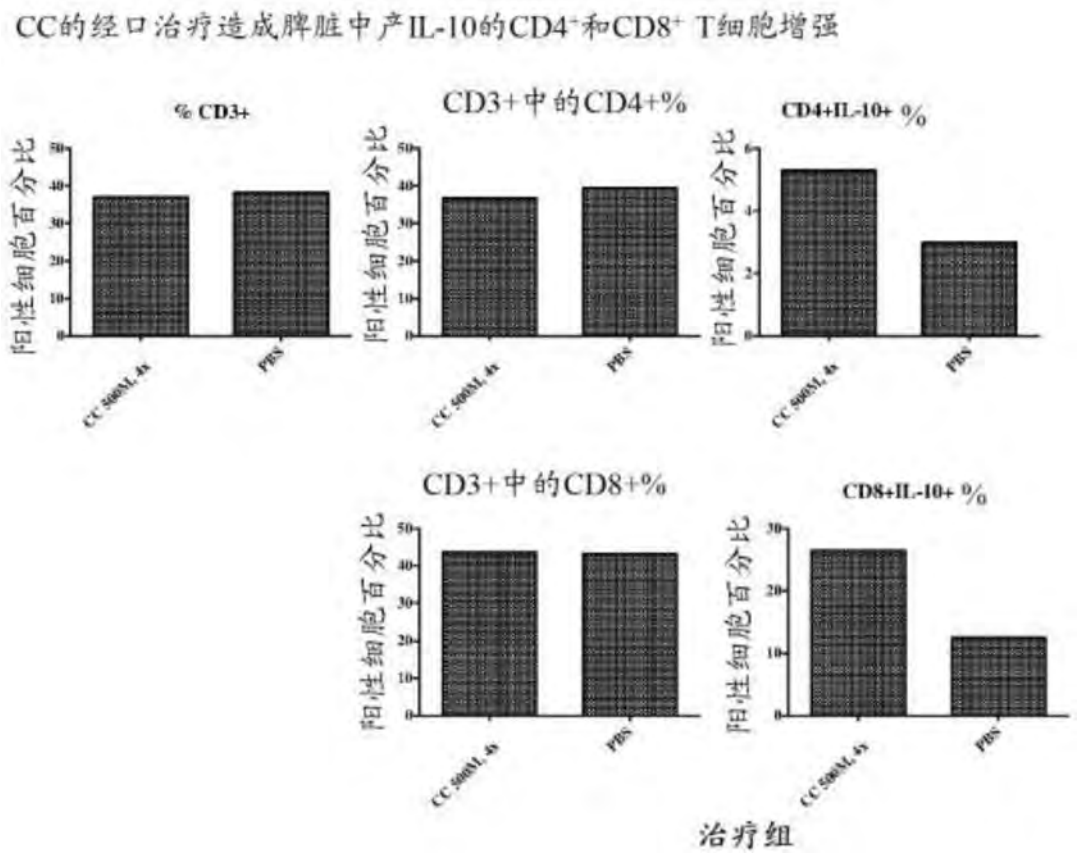

CC的经口治疗造成脾脏中产IL-10的CD4+和CD8+ T细胞增强
% CD3+
CD3+中的CD4+%
CD4+IL-10+ %
CD3+中的CD8+%
CD8+IL-10+ %
阳性细胞百分比
CC 500M, 4x
PBS
治疗组

图6

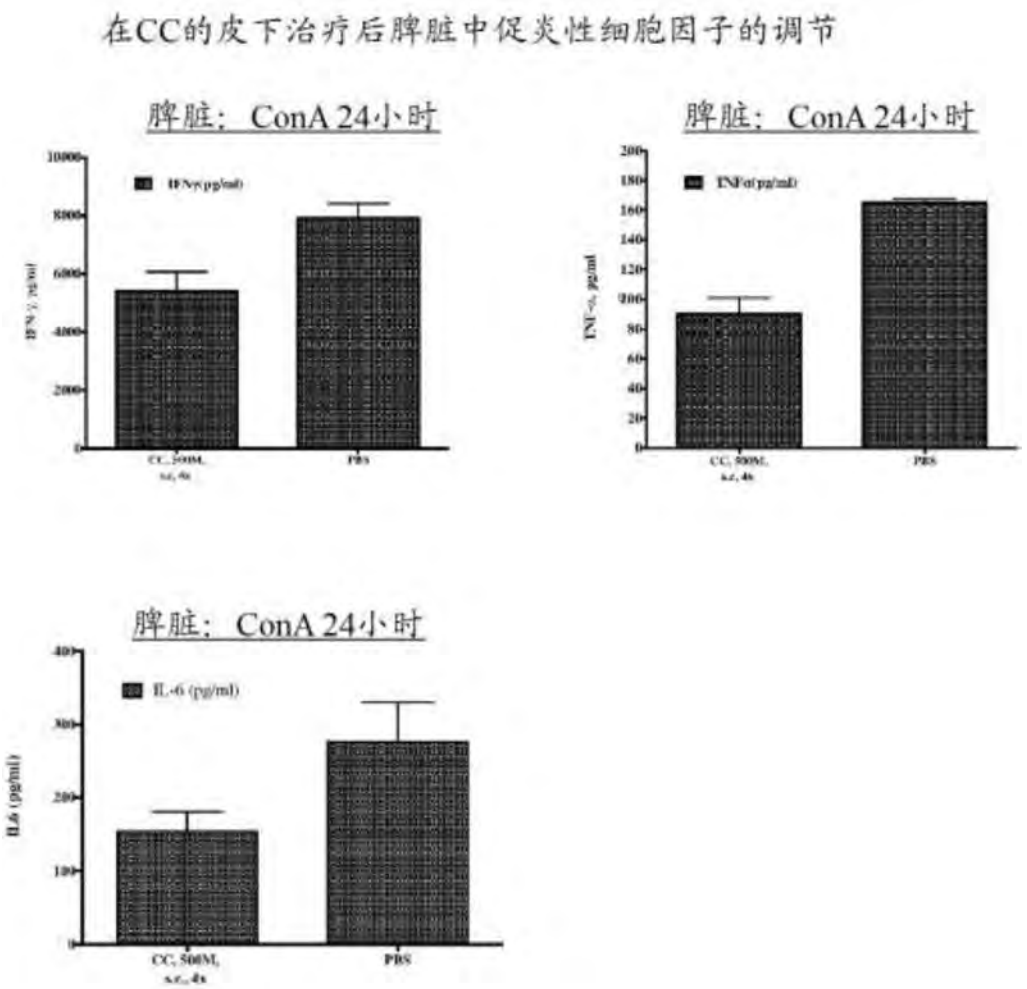

在CC的皮下治疗后脾脏中促炎性细胞因子的调节
脾脏：ConA 24小时
IFNγ(pg/ml)
CC, 50ML
PBS
脾脏：ConA 24小时
TNFα(pg/ml)
CC, 50ML
PBS
脾脏：ConA 24小时
IL-6 (pg/ml)
CC, 50ML
PBS

图7

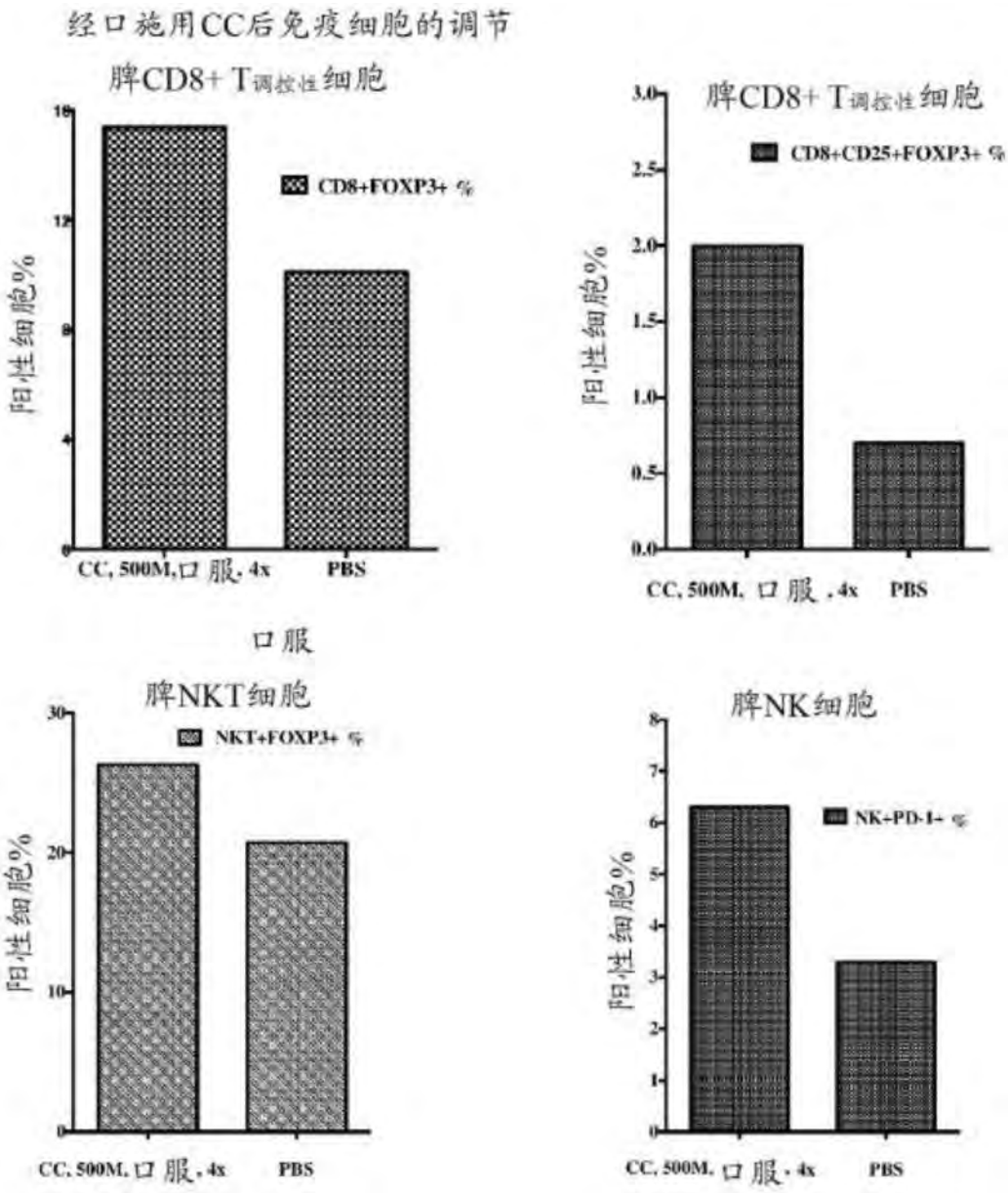

经口施用CC后免疫细胞的调节
脾CD8+ T调控性细胞
CD8+FOXP3+ %
阳性细胞%
CC, 500M,口 服, 4x
PBS
脾CD8+ T调控性细胞
CD8+CD25+FOXP3+ %
阳性细胞%
CC, 500M, 口 服 , 4x
PBS
口服
脾NKT细胞
NKT+FOXP3+ %
阳性细胞%
CC, 500M, 口 服 , 4x
PBS
脾NK细胞
NK+PD-1+ %
阳性细胞%
CC, 500M, 口 服 , 4x
PBS

图8

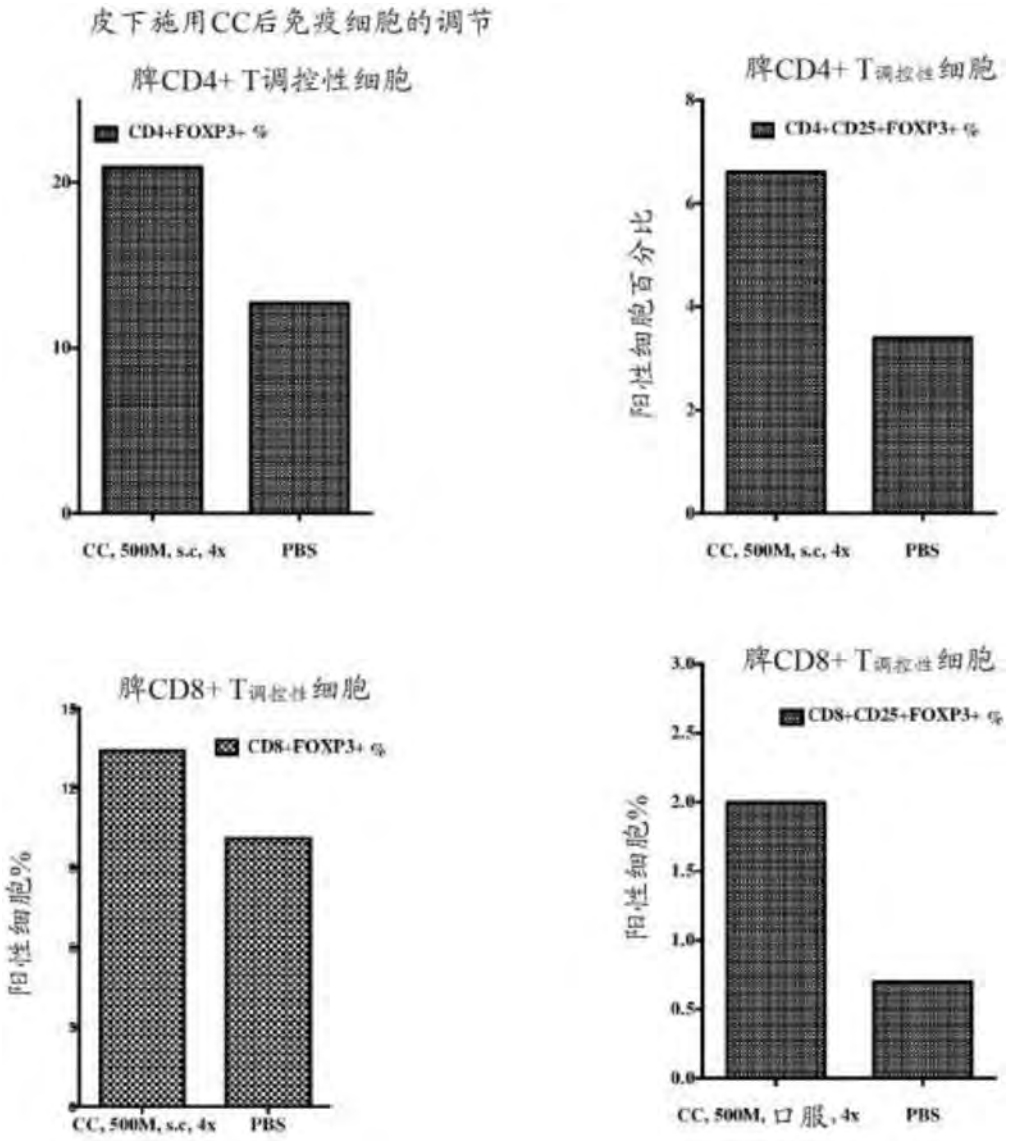

皮下施用CC后免疫细胞的调节
脾CD4+ T调控性细胞
CD4+FOXP3+ %
20
10
0
CC, 500M, s.c, 4x
PBS
脾CD4+ T调控性细胞
CD4+CD25+FOXP3+ %
阳性细胞百分比
8
6
4
2
0
CC, 500M, s.c, 4x
PBS
脾CD8+ T调控性细胞
CD8+FOXP3+ %
阳性细胞%
15
12
9
6
3
0
CC, 500M, s.c, 4x
PBS
脾CD8+ T调控性细胞
CD8+CD25+FOXP3+ %
阳性细胞%
3.0
2.5
2.0
1.5
1.0
0.5
0.0
CC, 500M, 口服, 4x
PBS

图9

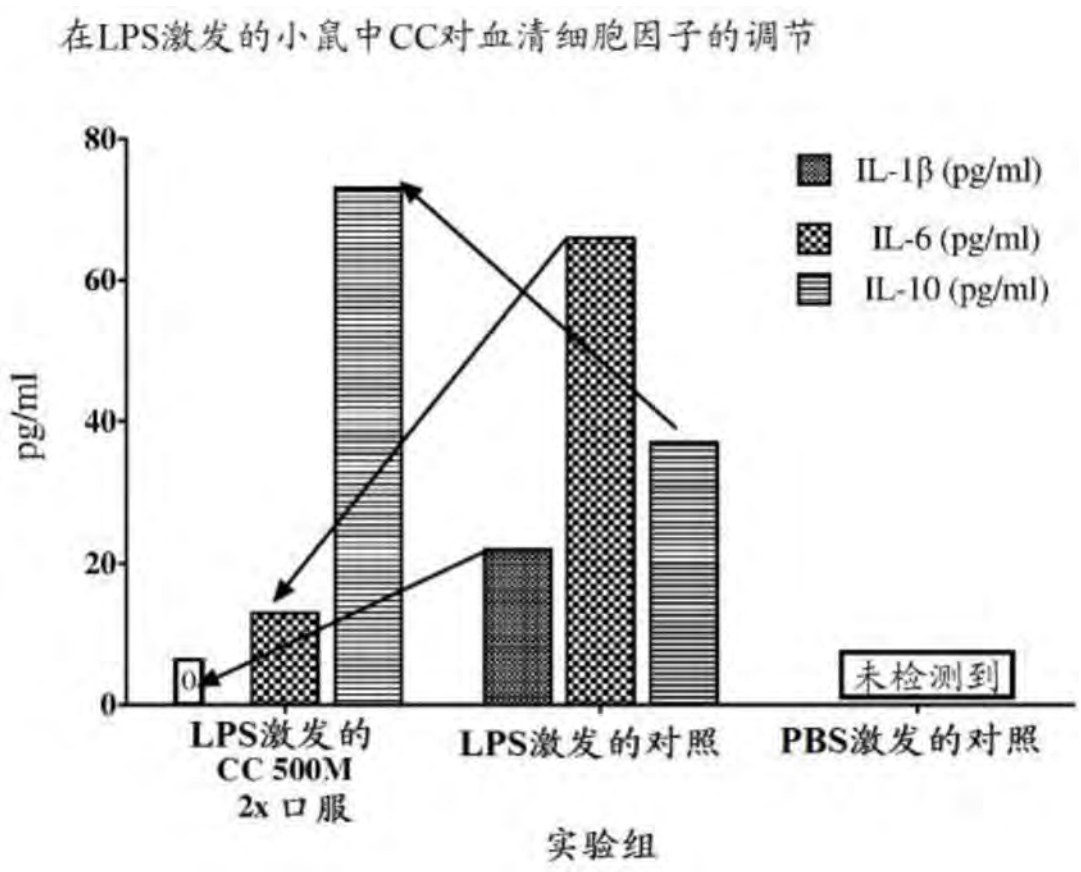

在LPS激发的小鼠中CC对血清细胞因子的调节
80
60
40
20
0
pg/ml
IL-1β (pg/ml)
IL-6 (pg/ml)
IL-10 (pg/ml)
0
未检测到
LPS激发的
CC 500M
2x 口服
LPS激发的对照
PBS激发的对照
实验组

图10

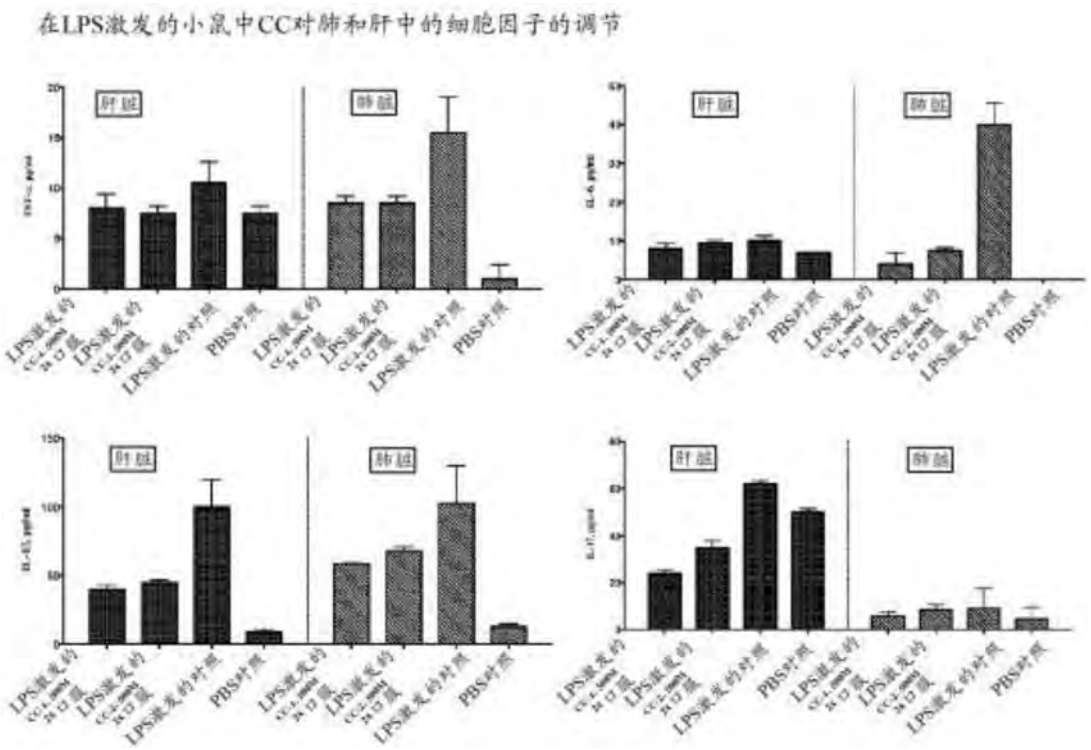

在LPS激发的小鼠中CC对肺和肝中的细胞因子的调节
肝脏
肺脏
LPS激发的
PBS对照

图11

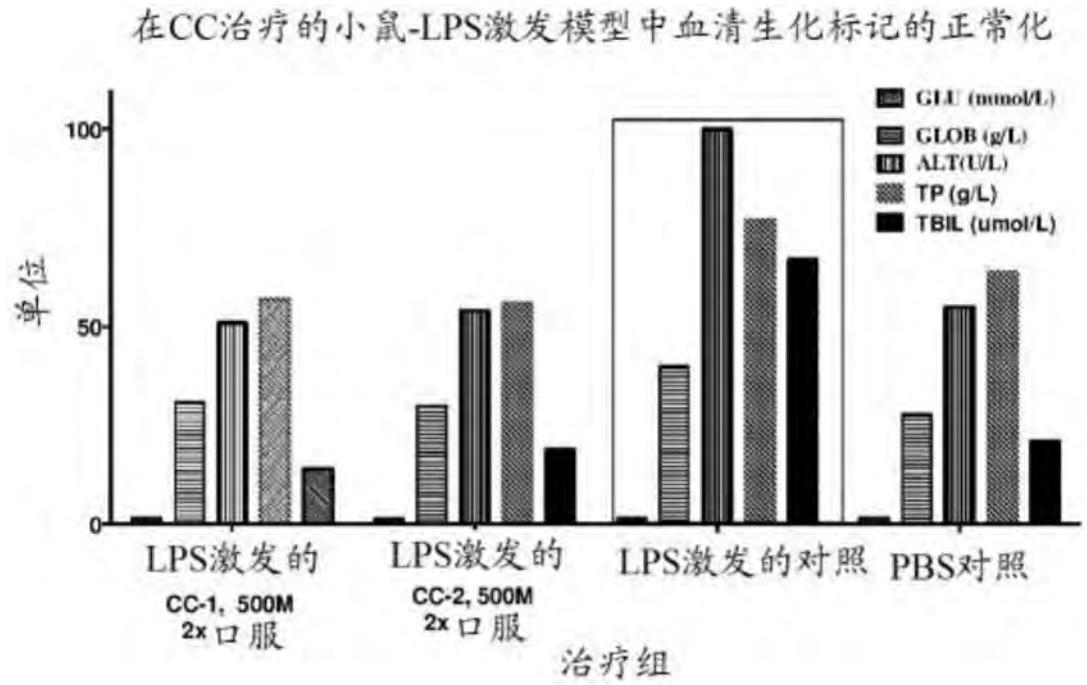

在CC治疗的小鼠-LPS激发模型中血清生化标记的正常化
GLU (mmol/L)
GLOB (g/L)
ALT(U/L)
TP (g/L)
TBIL (umol/L)
单位
100
50
0
LPS激发的
CC-1, 500M
2x口服
LPS激发的
CC-2, 500M
2x口服
LPS激发的对照
PBS对照
治疗组

图12

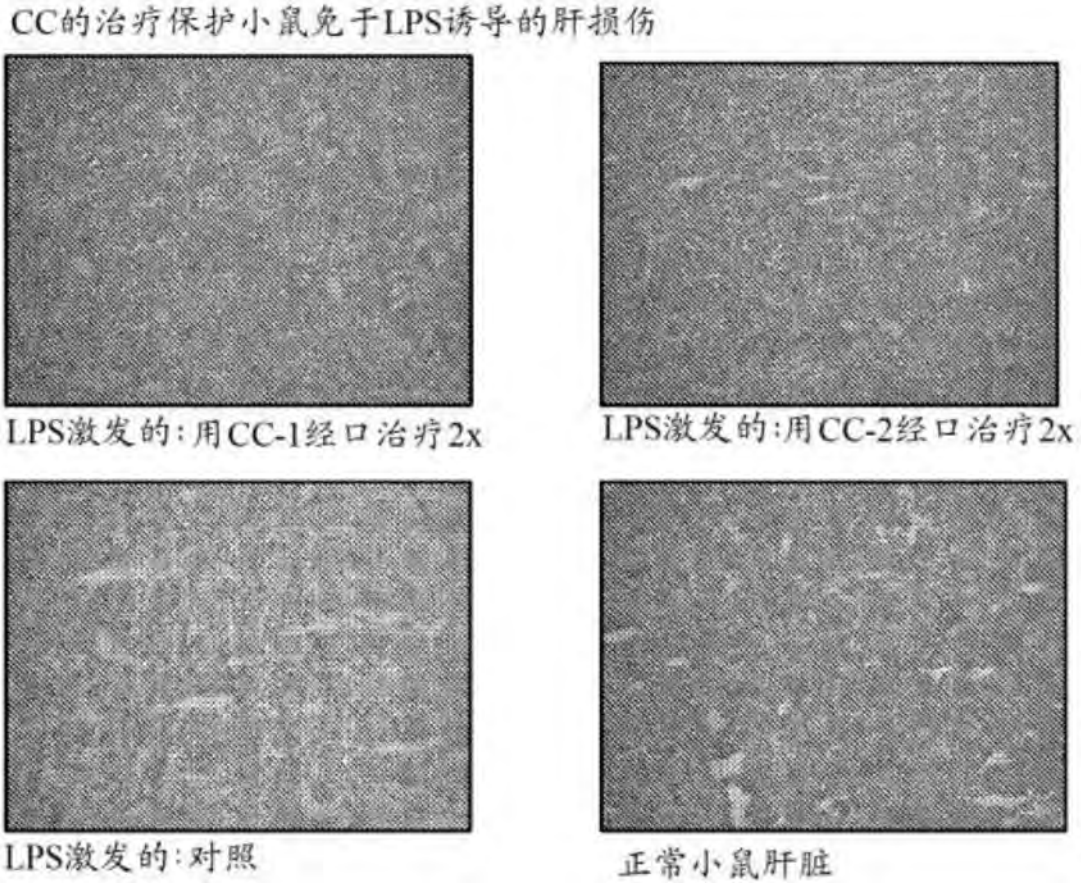

CC的治疗保护小鼠免于LPS诱导的肝损伤
LPS激发的:用CC-1经口治疗2x
LPS激发的:用CC-2经口治疗2x
LPS激发的:对照
正常小鼠肝脏

图13

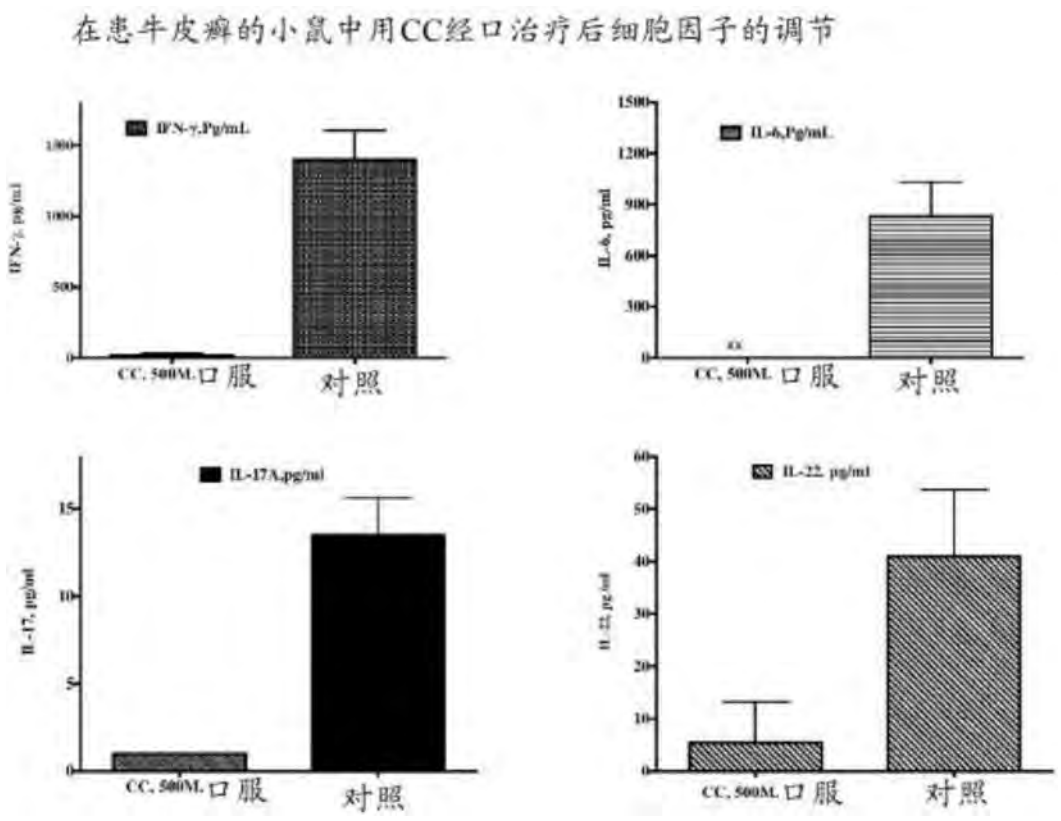

在患牛皮癣的小鼠中用CC经口治疗后细胞因子的调节
IFN-γ,Pg/mL
CC, 500ML口服
对照
IL-6,Pg/mL
CC, 500ML口服
对照
IL-17A,pg/ml
IL-17, pg/ml
CC, 500ML口服
对照
IL-22, pg/ml
CC, 500ML口服
对照

图14

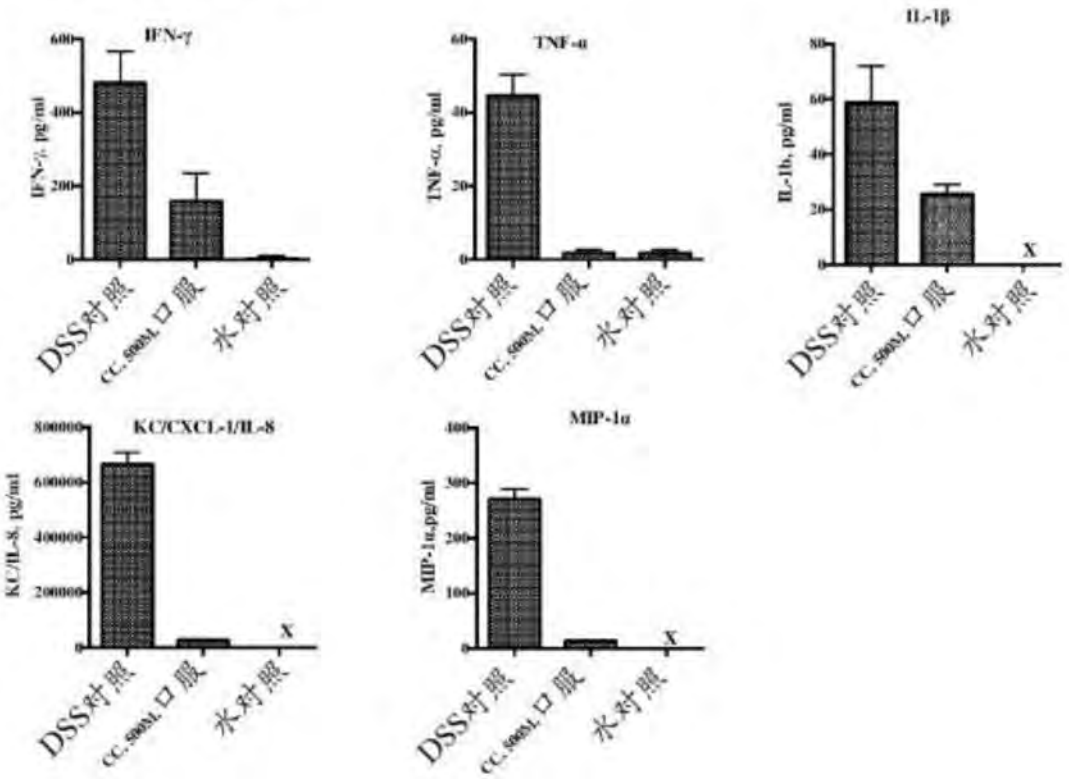

CC的经口治疗减少患DSS诱导的IBD的小鼠的结肠组织中的促炎性细胞因子和趋化因子
IFN-γ
IFN-γ, pg/ml
TNF-α
TNF-α, pg/ml
IL-1β
IL-1b, pg/ml
KC/CXCL-1/IL-8
KC/IL-8, pg/ml
MIP-1α
MIP-1α,pg/ml
DSS对照
CC, 500μL 口服
水对照

图15

CC的经口治疗在实验性自身免疫性脑脊髓炎(EAE)模型中抑制自身抗原特异性T细胞和抗体应答

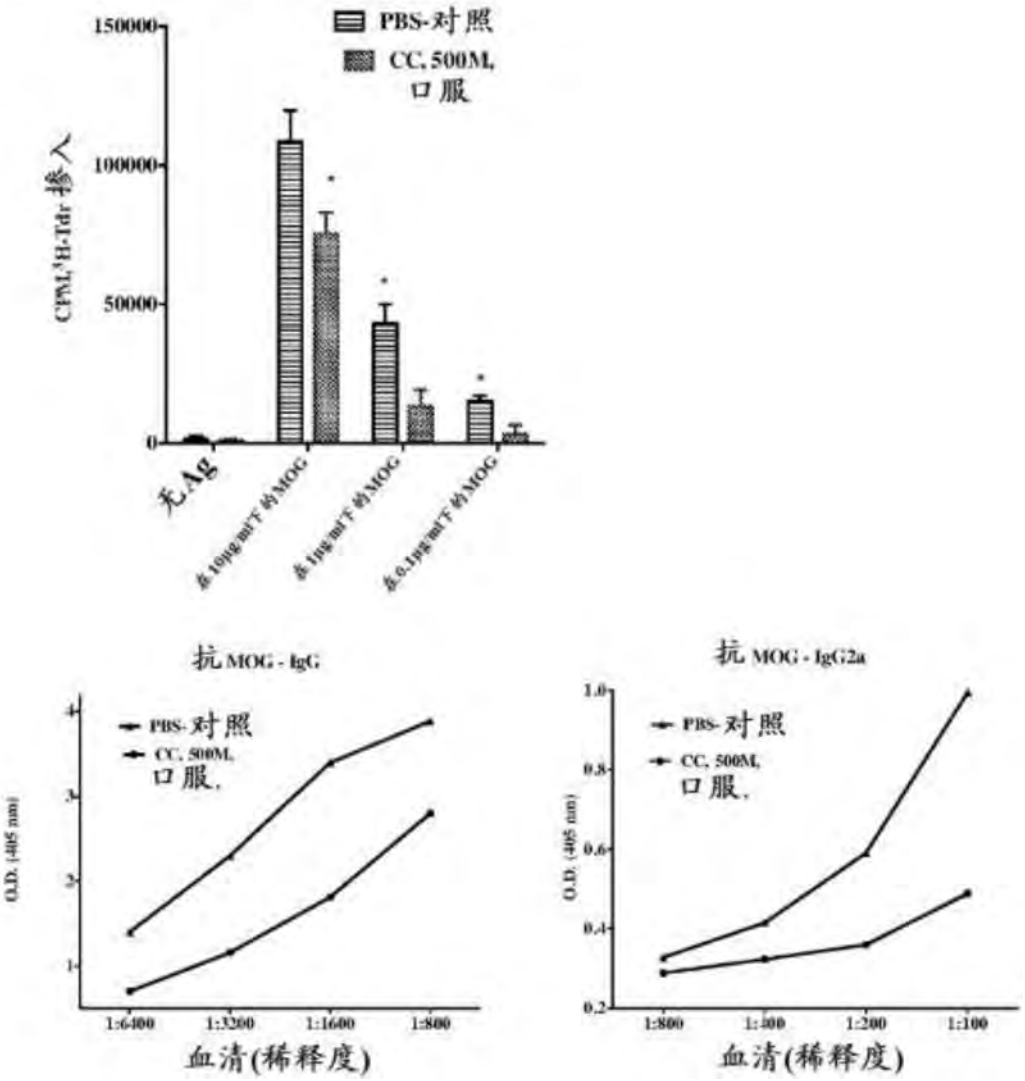


图16

CC的经口治疗在卵清蛋白诱导的气道炎症模型中抑制血清和肺洗出液中过敏原(OVA)特异性IgE的水平

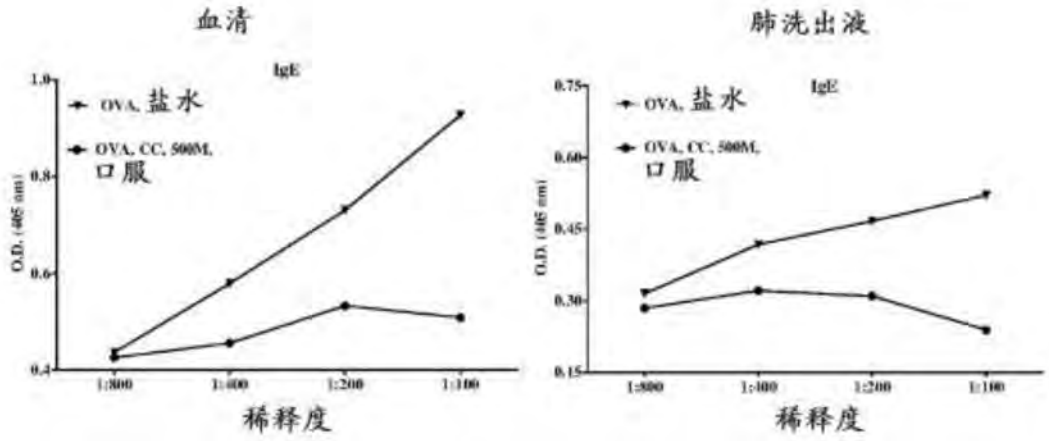


图17

CC的经口治疗在鼠模型中减少脾中的过敏原(OVA)特异性细胞因子(IL-4和IL-6)

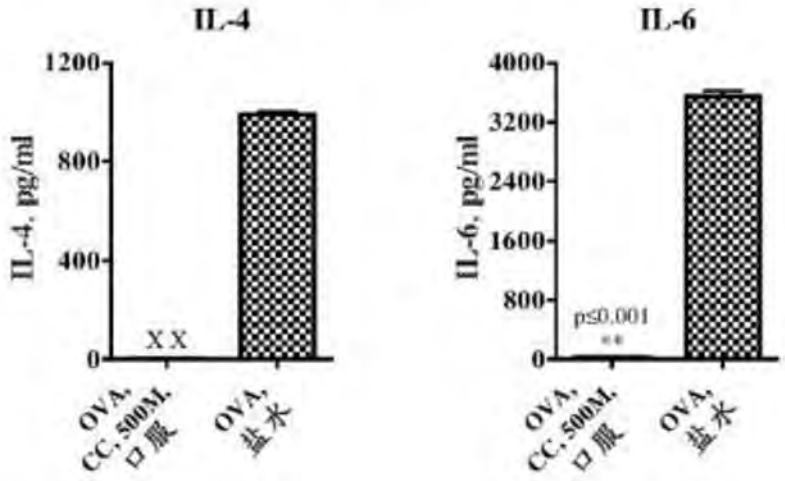


图18

与单独的地塞米松(DEX)相比，CC与DEX组合的经口治疗在OVA诱导的过敏性气道炎症模型中提供脾中的IL-4和IL-6水平降低的增强

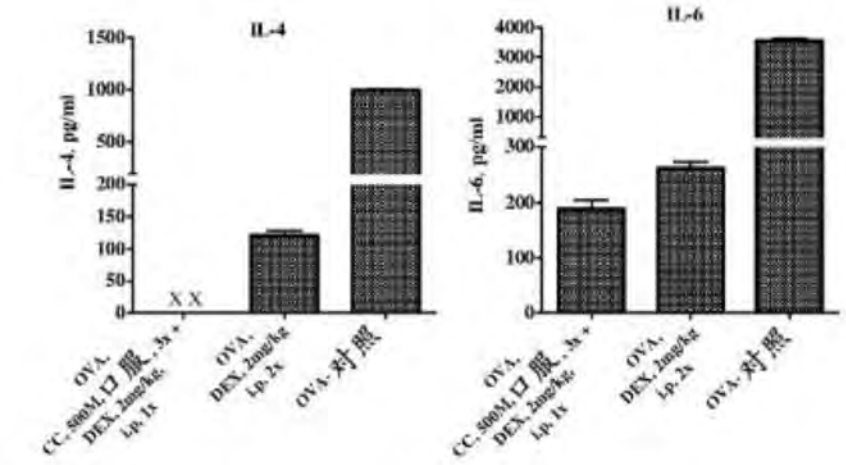


图19

CC的经口治疗减少高脂饮食饲喂小鼠的肝脏中促炎性细胞因子的产生

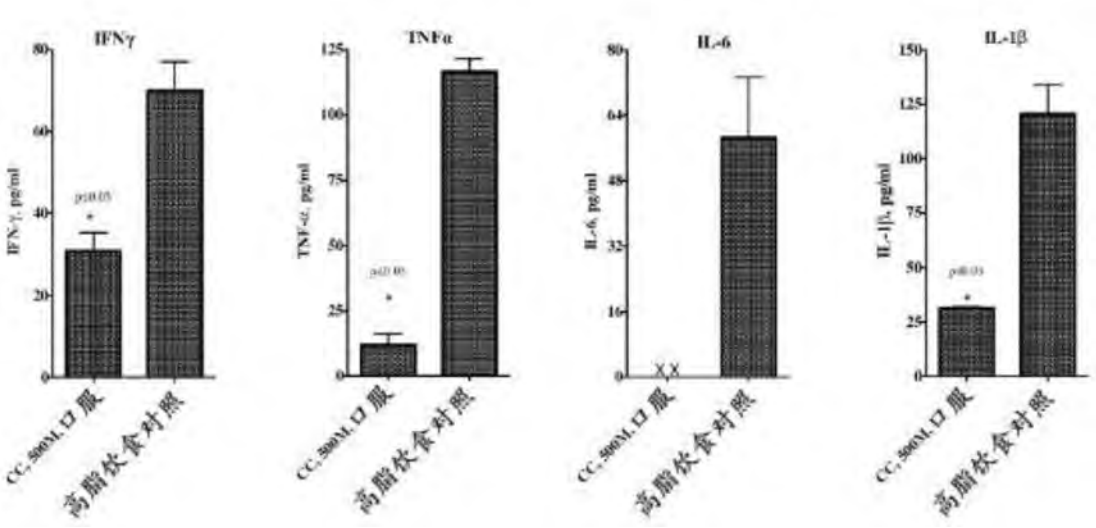


图20

CC的经口治疗抑制饮食诱导的肥胖小鼠的脾脏中的促炎性细胞因子

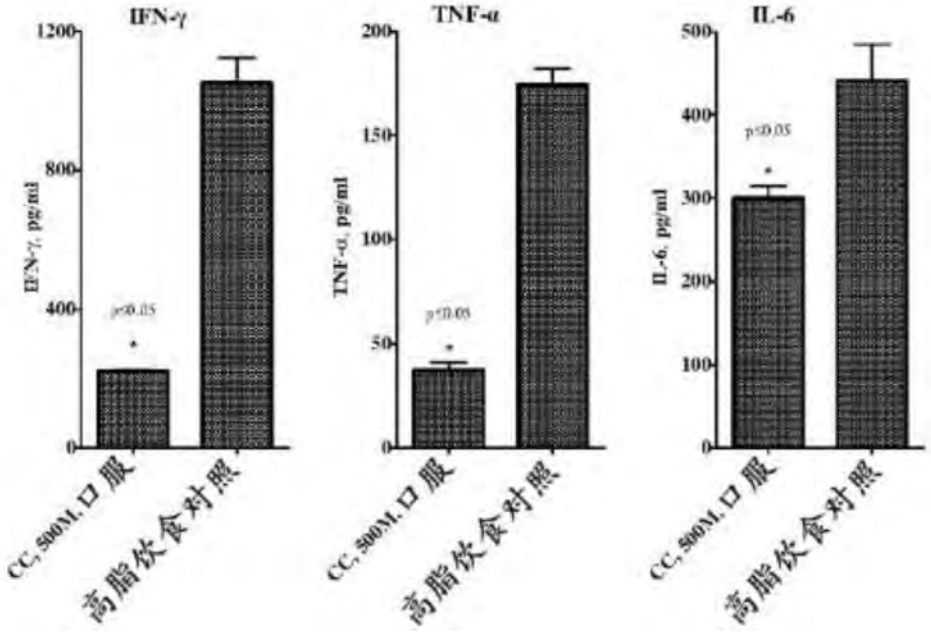


图21

CC的经口治疗在饮食诱导的肥胖模型中对代谢疾病的血清生化标记展现积极益处

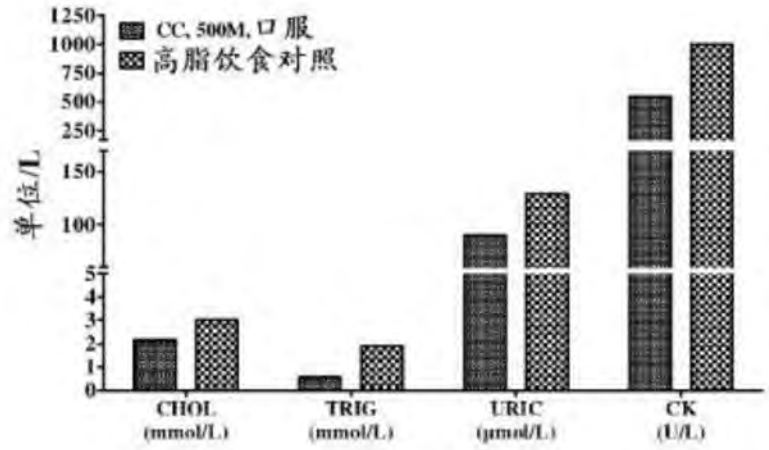


图22

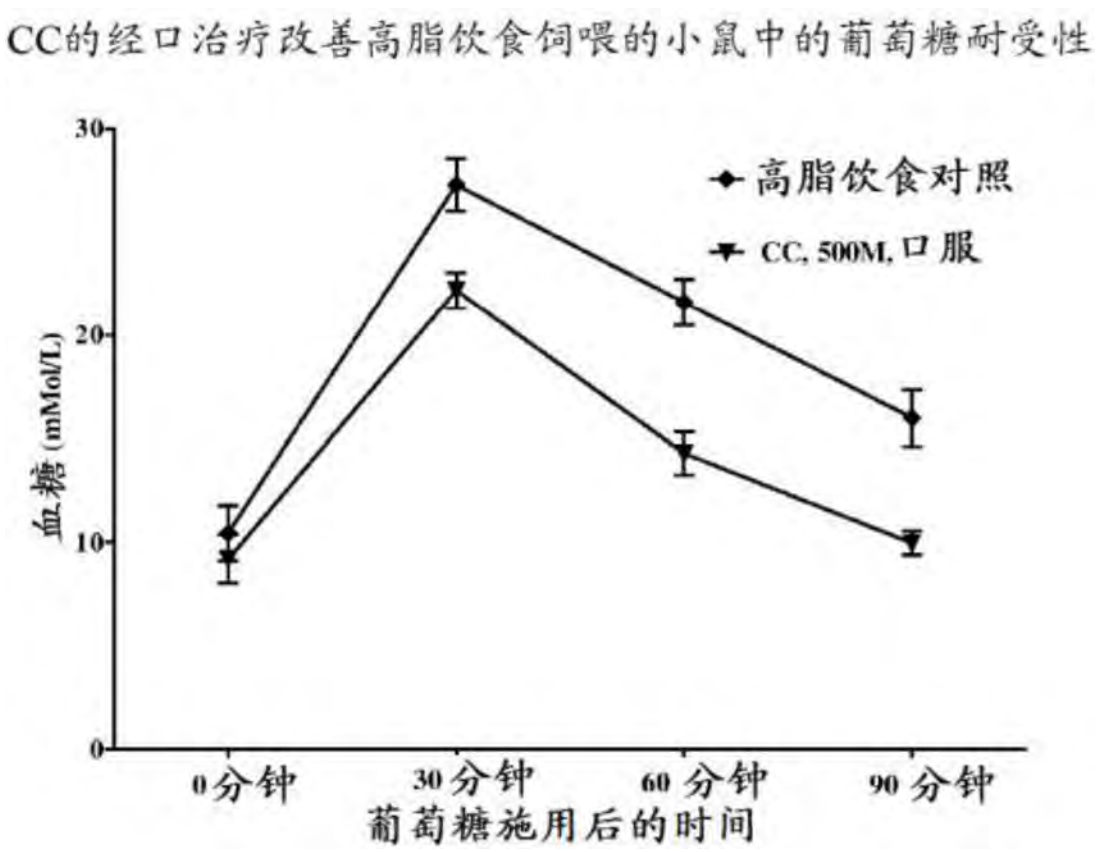

CC的经口治疗改善高脂饮食饲喂的小鼠中的葡萄糖耐受性
高脂饮食对照
CC, 500M, 口服
血糖 (mMol/L)
30
20
10
0
0分钟
30分钟
60分钟
90分钟
葡萄糖施用后的时间

图23

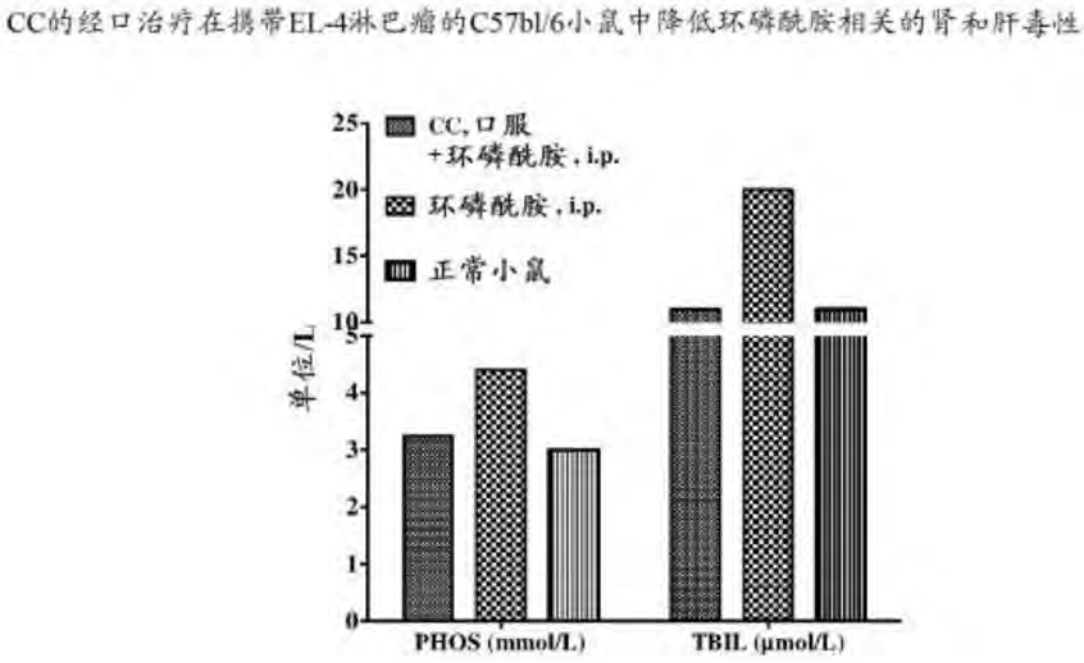

CC的经口治疗在携带EL-4淋巴瘤的C57bl/6小鼠中降低环磷酰胺相关的肾和肝毒性
CC, 口服
+环磷酰胺, i.p.
环磷酰胺, i.p.
正常小鼠
单位/L
25
20
15
10
5
4
3
2
1
0
PHOS (mmol/L)
TBIL (μmol/L)

图24

CC的经口治疗在B16转移性癌症模型中降低顺铂相关的肾和肝毒性

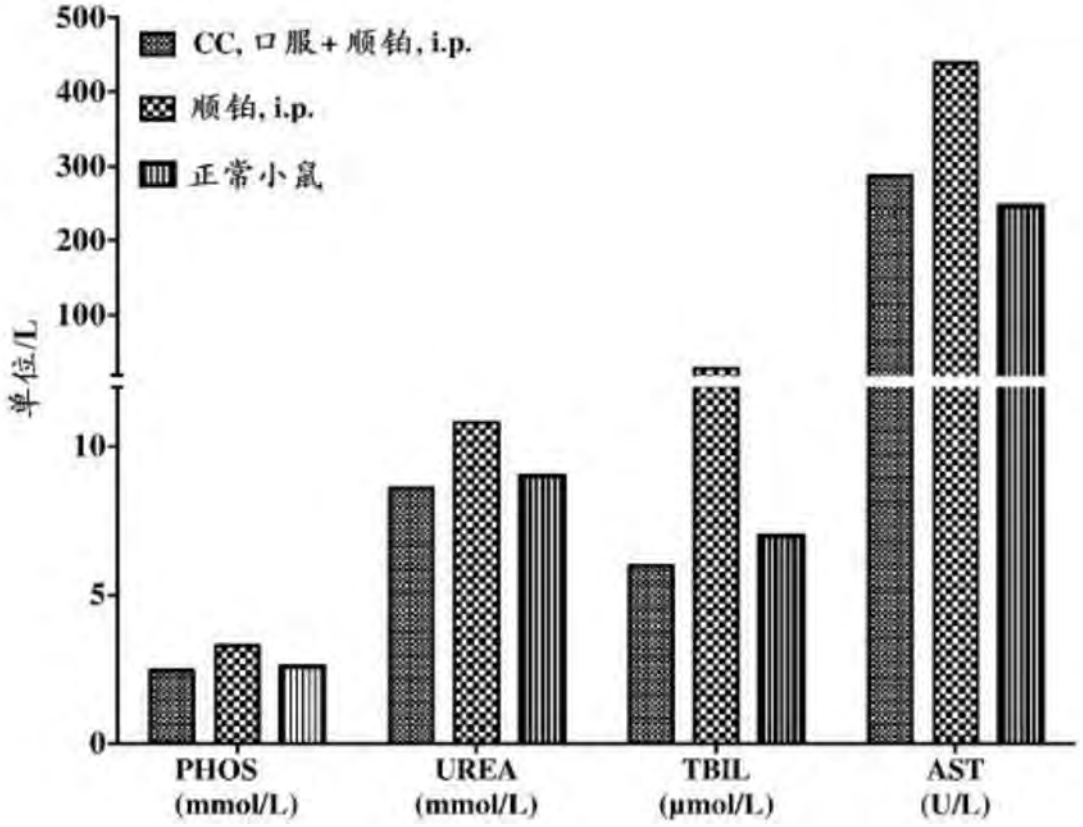


图25

CC的经口治疗在携带B16肿瘤的C57bl/6小鼠中降低抗PD1单克隆抗体相关的肝毒性

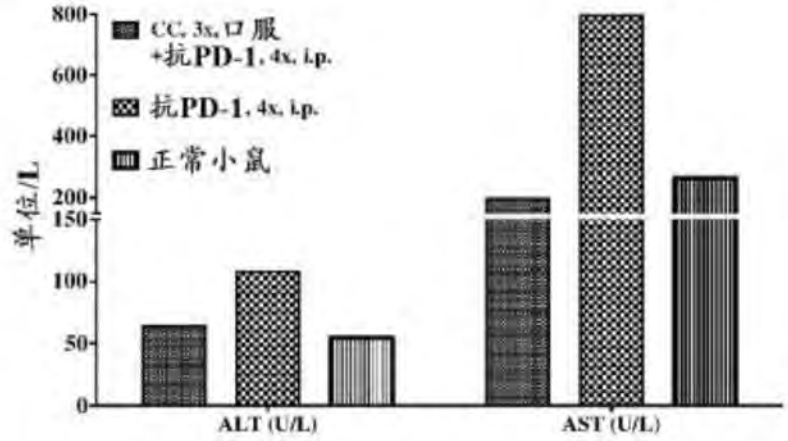


图26

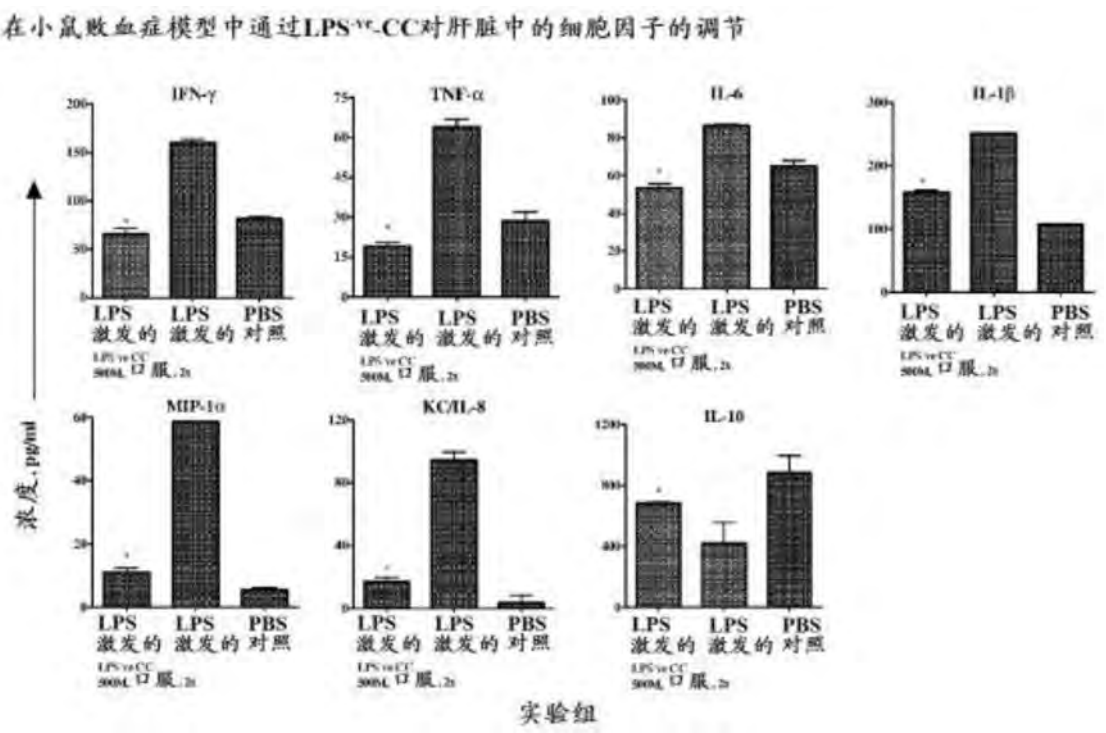

在小鼠败血症模型中通过LPS^ve-CC对肝脏中的细胞因子的调节
IFN-γ
TNF-α
IL-6
IL-1β
MIP-1α
KC/IL-8
IL-10
浓度，pg/ml
LPS 激发的
LPS 激发的
PBS 对照
实验组

图27

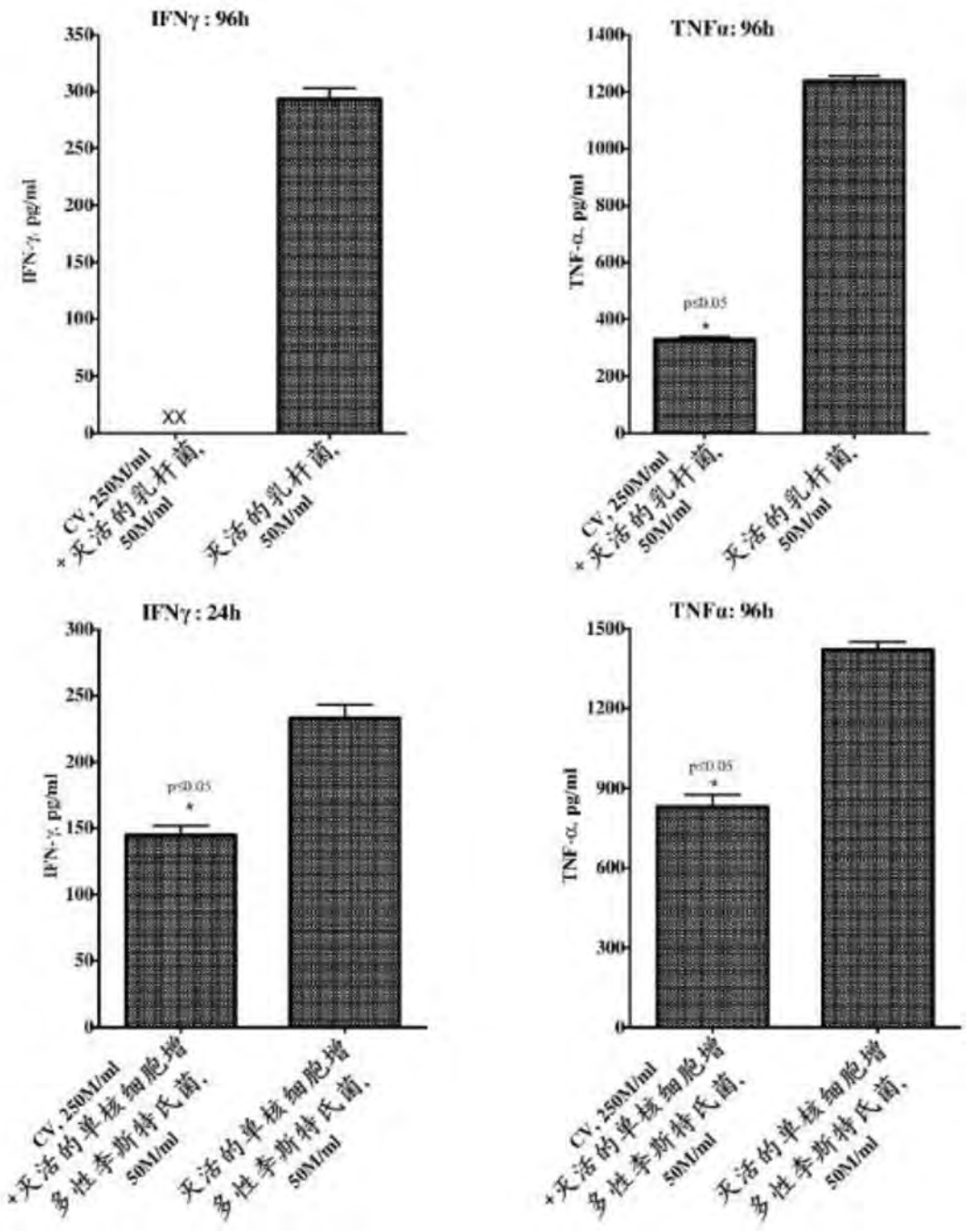

弧形柄杆菌(CV)减少人PBMC中由益生菌(鼠李糖乳杆菌)或致病细菌(单核细胞增多性李斯特氏菌)诱导的促炎性细胞因子
IFNγ : 96h
IFN-γ, pg/ml
XX
CV, 250M/ml
+灭活的乳杆菌,
50M/ml
灭活的乳杆菌,
50M/ml
TNFα: 96h
TNF-α, pg/ml
p<0.05
*
IFNγ : 24h
IFN-γ, pg/ml
p<0.05
*
CV, 250M/ml
+灭活的单核细胞增
多性李斯特氏菌,
50M/ml
灭活的单核细胞增
多性李斯特氏菌,
50M/ml
TNFα: 96h
TNF-α, pg/ml
p<0.05
*

图28

CC离体调节人树突细胞(DC)

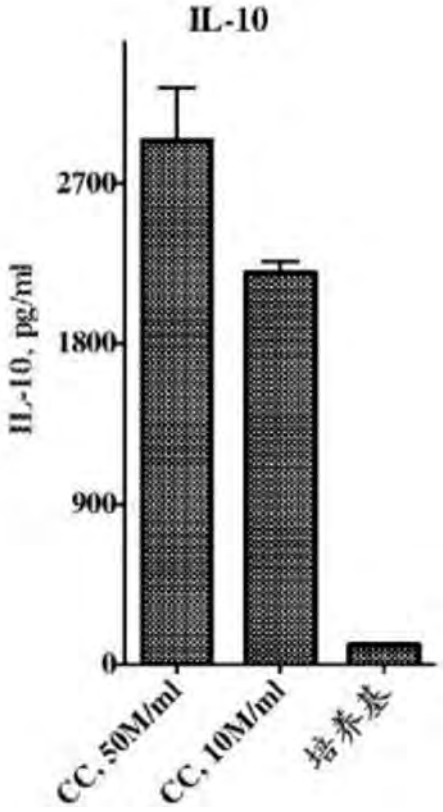


图29

CC造成来自人PBMC的多能干细胞(HSC，$CD34^+$)分化/扩增为髓性细胞

组	总$CD34^+CD45^-$	$CD34^+CD45^-$ $CD11c^-$	$CD34^+CD45^-$ $CD11b^A$
CC, $500x10^6$/ml	1.3	14	11.2
CC, $50x10^6$/ml	1.3	10.7	13.2
CC, $10x10^6$/ml	0.9	7.2	7.2
CC, $1x10^6$/ml	0.9	2	0.7
盐水	0.9	1.2	2

图30