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(54) Title: SHORT CHAIN FATTY ACIDS AND THEIR DERIVATIVES FOR USE IN TREATMENT IMMUNOGENIC DISORDERS

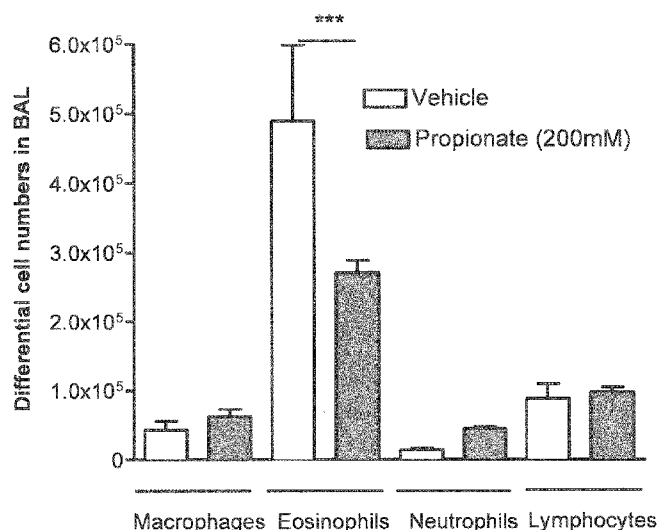


FIGURE 11

(57) Abstract: The present invention relates to short chain fatty acids (SCFA) for modulating a Th2 immune response towards a Th1 immune response for prevention and/or amelioration of viral infections and as an adjuvant for promoting the efficiency of vaccines and/or prevention of allergic diseases or disorders, particularly of a disease or disorder mediated by T helper 2 (Th2) cell-derived cytokines, including, without being limited to, IL-4, IL-5, IL-6, IL-8, IL-10 and IL-13, but particularly for use in the treatment of IL-4 and/or IL-8 and/or IgE mediated diseases or disorders and/or eosinophilic diseases or disorders.



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SHORT CHAIN FATTY ACIDS AND THEIR DERIVATIVES FOR USE IN TREATMENT OF IMMUNOGENIC DISORDERS

The present invention relates to short chain fatty acids (SCFA) for modulating an immune response. In particular, compositions and methods are provided for use in the treatment, prevention or attenuation of viral infections and/or virus-induced exacerbations of allergy or autoimmunity. In a second aspect, compositions and methods are provided for use in the prevention of development of a Th2 induced inflammatory condition in a tissue or organ of a subject.

Inefficient or misdirected immune responses are responsible for a broad range of human diseases and disorders. It is commonly accepted that an inappropriate Th1 cell driven immune response can be the reason for insufficient virus clearing and the development of autoimmune and allergic diseases or disorders.

Furthermore, cytokine compositions play also an important role in the chronic inflammation of allergic diseases such as, for example, asthma and play a critical role in orchestrating the allergic inflammatory response. Of particular importance to allergic disease is the recent recognition of the regulation of helper immune function by two lineages of T helper cells, i.e., Th1 and Th2, by these cytokines. The Th2 hypothesis of allergy considers atopy as a Th2-driven hypersensitivity reaction to allergens of complex genetic and environmental origins, in which the Th1 lineage, normally driven by IL-2, TNF, and IFN- γ is deficient, and in which a predominant Th2 response is seen that is mediated by IL-4, IL-13, IL-5, and IL-10.

Literature shows that Th2 lymphocytes are presently considered the main orchestrator of allergic airway inflammation underlying asthma. Functional analysis of the role of cytokines, largely based on *in vivo* animal models, confirms this hypothesis. During T cell differentiation from naive T cells into Th1 and Th2 cells, the expression of IL-10 in Th1 cells slowly disappear, whereas Th2 cells produce more IL-10. In contrast, Th2 cells secrete IL-4, IL-5, IL-9, IL-10, and IL-13, which are involved in isotype switching of B cells as well as proliferation and differentiation into antibody-secreting plasma cells. Interleukin-4 and IL-10 are also regulatory cytokines, antagonizing the activities of Th1 cytokines. Thus, the nature, intensity and duration of a specific immune response depend on the delicate balance between Th1 and Th2 numbers or activities (or both).

In particular, IL-4 and IL-13 are involved in the isotype switch from IgM to IgE, the antibody responsible for classic allergy and implicated in the pathophysiology of allergic asthma. Excessive IL-4 production by Th2 cells has been associated with elevated IgE production and allergy.

Recent studies with gene knockout mice have demonstrated that T helper 2 (Th2) cell-derived cytokines, including IL-4, IL-5, and IL-13, play important roles in causing allergic airway inflammation. *In vitro*, IL-4 is necessary for differentiation of the naive CD-positive T-cells within the Th2 subpopulation secreting IL-4, IL-5, IL-6, IL-10 and IL-13. Although IL-4 induces IgE synthesis and enables the immediate type of hypersensitivity reaction, there is certain evidence suggesting *in vitro* and *in vivo* anti-inflammatory effects of IL-4. IL-4 is critical in switching B lymphocytes to produce IgE, for expression of VCAM-1 on endothelial cells, and for inducing the differentiation of Th2 cells and IL-5, which is essential for the differentiation of eosinophils.

The critical role of IL-5 in eosinophilia has been confirmed by the use of an anti-IL-5 antibody in asthmatic patients, which almost depletes circulating eosinophils and prevents eosinophil recruitment into the airway after allergen. IL-5 is a cytokine that is not encountered at high levels in healthy individuals. The control of IL-5 protein production takes place at the level of transcription. IL-10 is a potent anti-inflammatory cytokine that inhibits the synthesis of many inflammatory proteins, including cytokines (TNF- α , granulocyte macrophage colony stimulating factor, IL-5, chemokines) and inflammatory enzymes (inducible nitric oxide synthase) that are over-expressed in asthma. In addition, IL-10 inhibits antigen presentation and sensitisation. IL-13 signals through the IL-4 receptor α -chain, but may also activate different intracellular pathways.

Thus, IL-4, IL-5 and IL-10 are of critical importance in the differentiation of Th2 cells and are therefore 'upstream' cytokines that are an attractive therapeutic target in the treatment of atopic diseases.

In addition to Th2 cytokines, IgE-dependent activation of mast cells has been suggested to play a role in allergic airway inflammation. Whereas IgE cross-linking by antigens did not induce eosinophil recruitment into the airways or airway hyperreactivity, IgE cross-linking induced T cell recruitment into the airways. In addition, when antigen-specific Th2 cells were transferred to IgE transgenic mice, IgE cross-linking significantly enhanced antigen-induced eosinophil recruitment into the airways. These findings suggest that IgE-dependent mast cell activation plays an important role in allergic airway inflammation by recruiting Th2 cells into the site of allergic inflammation.

Eosinophils are believed to be the final effector cells in the pathogenesis of allergic disease and bronchial asthma. These cells also have the capacity to synthesize and release a wide array of cytokines. Eosinophils can also secrete TGF- α and TGF- β and as such may account for the eosinophil-derived stimulatory capacity for fibroblast proliferation, which leads to changes in the lung architecture and thus may contribute to the irreversibility of bronchial asthma. Likewise, human eosinophils synthesize and secrete IL-6, which facilitates IL-4 dependent IgE production (Coyle and Tsuyuki, 1995).

The IL-4 cytokine released from Th2 and Th2-like cells is likely to be central to the pathophysiology of asthma and allergy in that it contributes to aberrant IgE production, eosinophilia and, perhaps, mucosal susceptibility to viral infections. Accordingly, it was suggested in Coyle and Tsuyuki (1995) that inhibitors of Th2 cytokine production will prove to be of therapeutic value. It was further suggested that inhibition of IL-4 may offer advantages in steroid resistant asthma by preventing/reversing impaired steroid receptor function and in viral mediated exacerbations of asthma, where IL-4 may be of central importance in switching cytotoxic CD8+ T cells to a Th2 like phenotype.

Viral infections are a major cause of worldwide morbidity and mortality. Acute and chronic viral infections cause direct pathology, but they can also influence other concurrent responses (e.g. exacerbations of allergy or allergic diseases or autoimmunity) or in fact shape the immune system in such a way that subsequent immune responses develop differently. Important examples are virally conferred protection or enhancement of allergy subsequent to infection, or the development of immunodeficiency in chronic infection.

For example, Respiratory-Syncytial-Virus (RSV) is a major respiratory pathogen that infects nearly all children by the age of 2 or 3; however, natural infection results in poor immunity and consequently people are not protected against subsequent infection. Severe prior infection with RSV has been linked with an increased susceptibility to the development of asthma although the molecular mechanisms remain to be fully elucidated. In addition, akin to Influenza virus infection, following RSV infection there is an increased susceptibility to bacterial infections and consequently impaired anti-bacterial responses. There are currently no vaccines available for RSV and prophylactic treatment with monoclonal antibodies are the primary source of protection for infants and the elderly.

It remains unclear how RSV manages to subvert protective immunity, and the mechanisms by which infection may predispose people to asthma remains highly debated. However, a tragic vaccine trial failure provided some key insight into the pathogenic mechanisms: young children vaccinated with formalin inactivated RSV developed a profound Th2-biased

immune response upon subsequent natural infection by RSV, which in some cases was fatal.

It is known that pathogens such as viruses activate CD8⁺ T cells. These cells typically produce a Th1 like cytokine panel (INF- γ , IL-2) after *in vitro* stimulation. CD8⁺ T cells are further known to mediate lysis of viral infected cells and inhibition of viral replication through the production of INF- γ .

However, it has recently been shown that viral antigen-specific activation of CD8⁺ T cells in the presence of IL-4 may lead to a switch of CD8⁺ T cells towards a Th2 like phenotype that produces IL-5 and reduced amounts of INF- γ . This phenotype switch may contribute to an exacerbation of asthma severity due to IL-5 production. Further, the reduced secretion of INF- γ may impair the normal host response, leading to delayed viral clearance from the lung. (Coyle and Tsuyuki (1995)).

Further viral infections leading to a worldwide morbidity and mortality are caused by influenza viruses and require seasonal vaccination.

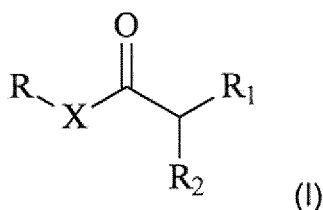
Even though vaccines against viral infections can be very effective, there is a clear need for improvements in terms of vaccine design and increased adjuvant efficiency to promote vaccine action. In particular, the possibility of utilizing an adjuvant which required less vaccine to elicit protection against infection would be high valuable especially during viral pandemics.

Accordingly, there is a desperate need for improved strategies for treating viral infections such as RSV and Influenza, and/or for preventing or ameliorating autoimmune diseases, allergic disorders/diseases.

This need could be satisfied within the scope of the present invention by providing compositions and methods for the modulation of a Th2 or Th2-like immune response towards a Th1 immune response, which leads to prevention or attenuation of viral infections and/or virus-induced exacerbations of allergy or autoimmunity and of allergic disorders in general.

In particular, short chain fatty acids according to the present invention can be used in human therapy for use in the treatment, prevention or attenuation of viral infections and/or virus-induced exacerbations of allergy or autoimmunity and the treatment, prevention or attenuation of allergic disorders in general.

The present invention now provides a compound of formula (I)



wherein

X represents -O-, -S-, or -NH-, preferably -O-;

R represents hydrogen, alkyl, aryl, arylalkyl, polyalkylene glycol;

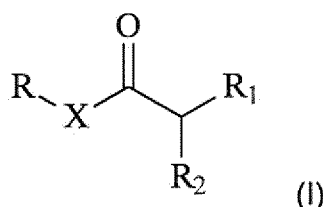
R₁ represents hydrogen, alkyl, hydroxyalkyl, arylalkylcarboxylic acid;

R₂ represents hydrogen, alkyl, -O-R₃; and

R₃ represents hydrogen, aryl, arylalkyl, hydroxyalkyl-carboxyl;

or pharmaceutically acceptable salts thereof, for modulation of a Th2 or Th2-like immune response towards a Th1 immune response.

In one embodiment, the present invention relates to a compound of formula (I)



wherein

X represents -O-, -S-, or -NH-, preferably -O-;

R represents hydrogen, alkyl, aryl, arylalkyl, polyalkylene glycol;

R₁ represents hydrogen, alkyl, hydroxyalkyl, arylalkylcarboxylic acid;

R₂ represents hydrogen, alkyl, -O-R₃; and

R₃ represents hydrogen, aryl, arylalkyl, hydroxyalkyl-carboxyl;

or pharmaceutically acceptable salts thereof, for use in the treatment, prevention or attenuation of viral infections and/or virus-induced exacerbations of allergy or autoimmunity.

The compound of formula (I) may also be used as an adjuvant for inducing, promoting or enhancing an immune response in a subject treated with an immunogen, for example, an immunogen comprised in a vaccine, particularly a viral vaccine.

In one embodiment, the compound of formula (I) is a compound, wherein

X represents -O-, -S-, or -NH-, preferably -O-;

R represents hydrogen, alkyl, aryl, arylalkyl, polyalkylene glycol;

R₁ represents hydrogen, alkyl, hydroxyalkylcarboxylic acid;

R₂ represents hydrogen, alkyl, -O-R₃; and

R₃ represents hydrogen, aryl, arylalkyl, hydroxyalkyl-carboxyl;
or pharmaceutically acceptable salts thereof.

In a specific embodiment the compound of formula (I) is a compound according to the invention and as described herein in the various embodiments, wherein

X represents -O-, -S-, or -NH-, preferably -O-;

R represents hydrogen, C₁-C₆ alkyl, unsubstituted or substituted phenyl with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano, C₁-C₄ alkyloxy or trifluoro;

R₁ represents hydrogencarboxylic acid, C₁-C₆ alkyl, hydroxy-C₁-C₆ alkyl wherein the alkyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of hydroxyl, amino, carboxylic acid, halogen, cyano, or nitro;

R₂ represents hydrogen, C₁-C₆ alkyl, -O-R₃; and

R₃ represents hydrogen, unsubstituted or substituted phenyl with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano, C₁-C₄ alkyloxy or trifluoro, phenyl-C₁-C₆ alkyl wherein the phenyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano, C₁-C₄ alkyloxy or trifluoro, hydroxy-C₁-C₆ alkyl-carboxyl;

or pharmaceutically acceptable salts thereof.

In another specific embodiment, the compound of formula (I) is a compound according to the invention and as described herein in the various embodiments, wherein

X is -O-,

R is hydrogen;

R₁ represents hydrogencarboxylic acid, C₁-C₄ alkyl, hydroxy-C₁-C₄ alkyl wherein the alkyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of hydroxyl, amino, or carboxylic acid, preferably hydroxyl and/or carboxylic acid; and

R₂ is hydrogen or C₁-C₄ alkyl;

or pharmaceutically acceptable salts thereof.

In another specific embodiment, the compound of formula (I) is a compound according to the invention and as described herein in the various embodiments, wherein

X is -O-,

R is hydrogen;

R₁ represents hydrogencarboxylic acid, C₁-C₄ alkyl, hydroxy-C₁-C₄ alkyl wherein the alkyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of hydroxyl, amino or carboxylic acid, preferably hydroxyl and/or carboxylic acid; and

R₂ is -OR₃; and

R₃ represents hydrogen, unsubstituted or substituted phenyl with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano or methoxy, phenyl-C₁-C₄ alkyl wherein the phenyl group may be unsubstituted or substituted with one or more, same or different substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano or methoxy, hydroxy-C₁-C₃ alkyl-carboxyl;

or pharmaceutically acceptable salts thereof.

In another specific embodiment, the compound of formula (I) is a compound according to the invention and as described herein in the various embodiments, wherein

X is -O-,

R is hydrogen;

R₁ represents hydrogencarboxylic acid, C₁-C₃ alkyl, hydroxy-C₁-C₃ alkyl wherein the alkyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of hydroxyl and/or carboxylic acid; and

R₂ is hydrogen or C₁-C₄ alkyl;

or pharmaceutically acceptable salts thereof.

In another specific embodiment, the compound of formula (I) is a compound according to the invention and as described herein in the various embodiments, wherein

X is -O-,

R is hydrogen;

R₁ represents hydrogen, carboxylic acid, C₁-C₃ alkyl, hydroxy-C₁-C₃ alkyl wherein the alkyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of hydroxyl or carboxylic acid;

R₂ is -OR₃; and

R₃ represents hydrogen, unsubstituted or substituted phenyl with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano or methoxy, phenyl-C₁-C₄ alkyl wherein the phenyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano, or methoxy, hydroxy-C₁-C₃ alkyl-carboxyl;

or pharmaceutically acceptable salts thereof.

In particular, the compound of formula (I) is a compound according to the invention and as described herein in the various embodiments, wherein

X is -O-,

R is hydrogen;

R₁ is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, isopropyl, hydroxymethyl, dihydroxymethyl, hydroxyethylcarboxylic acid, carboxylic acidmethylcarboxylic acid, hydroxymethylcarboxylic, ethylcarboxylic acid; and

R₂ is selected from the group consisting of hydrogen, hydroxyl or methyl;

or pharmaceutically acceptable salts thereof, or wherein

X is -O-,

R is hydrogen;

R₁ is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, isopropyl;

R₂ is -OR₃; and

R₃ is selected from the group consisting of 1-hydroxyethylcarbonyl, benzyl, nitrophenyl; or pharmaceutically acceptable salts thereof.

In yet another specific embodiment, the compound of formula (I) is a compound according to the invention and as described herein in the various embodiments, wherein

X is -O-,

R represents C₁-C₄ alkyl, unsubstituted or substituted phenyl with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano or methoxy, phenyl-C₁-C₄ alkyl wherein the phenyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of halogen, nitro, amino, hydroxyl, cyano or methoxy, polyalkylene glycol;

R₁ is carboxylic acid, C₁-C₄ alkyl or hydroxy-C₁-C₄ alkyl, wherein the alkyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of hydroxyl, amino or carboxylic acid; and

R₂ is hydrogen;

or pharmaceutically acceptable salts thereof

In yet another specific embodiment, the compound of formula (I) is a compound according to the invention and as described herein in the various embodiments, wherein

X is -O-,

R represents C₁-C₄ alkyl, unsubstituted or substituted phenyl with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano or methoxy, phenyl-C₁-C₄ alkyl wherein the phenyl group may be

unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of halogen, nitro, amino, hydroxyl, cyano or methoxy, polyalkylene glycol;

R₁ is carboxylic acid, C₁-C₃ alkyl or hydroxy-C₁-C₃ alkyl wherein the alkyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of hydroxyl and/or carboxylic acid; and

R₂ is hydrogen;

or pharmaceutically acceptable salts thereof.

In particular, the invention the compound of formula (I) is a compound according to the invention and as described herein in the various embodiments, wherein

X is -O-,

R is selected from the group consisting of methyl, ethyl, propyl, benzyl, nitrobenzyl, polyethylene glycol;

R₁ selected from the group consisting of ethyl, hydroxyethyl, methyl, hydroxymethyl; and

R₂ is hydrogen;

or pharmaceutically acceptable salts thereof

The still another specific embodiment, the compound of formula (I) is a compound according to the invention and as described herein in the various embodiments selected from the group consisting of acetic acid, propionic acid, butyric acid, isobutyric acid, 2-hydroxypropionic acid, dilactic acid, 2-benzoyloxypropionic acid, 2-(*p*-nitrophenyl)-oxypropionic acid, 3-hydroxypropionic acid, 2,3-dihydroxypropionic acid, methyl 3-hydroxypropionate, ethyl 3-hydroxypropionate, propyl 3-hydroxypropionate, benzyl 3-hydroxypropionate, para-nitrophenyl 3-hydroxypropionate, *p*-nitrobenzyl 3-hydroxypropionate, polyethylene glycol 3-hydroxypropionate, methyl propionate, ethyl propionate, propyl propionate, benzyl propionate, *p*-nitrophenyl propionate, *p*-nitrobenzyl propionate, 2-(4-Isobutylphenyl) propionic acid, lactic acid, citric acid, malic acid, malonic acid, succinic acid, and tartaric acid; or pharmaceutically acceptable salts thereof.

In still another embodiment of the invention, the compound for use according to the invention and as described herein in the various embodiments is selected from the group consisting of propionic acid, isobutyric acid, 3-hydroxypropionic acid, 2,3-dihydroxypropionic acid, lactic acid, or citric acid.

The compounds of this invention may contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of these compounds are expressly

included in the present invention. The compounds of this invention may also contain linkages (e. g., carbon- carbon bonds) wherein bond rotation is restricted about that particular linkage, e. g. restriction resulting from the presence of a ring or double bond. Accordingly, all cis-trans and E/Z isomers are expressly included in the present invention. The compounds of this invention may also be represented in multiple tautomeric forms, in such instances, the invention expressly includes all tautomeric forms of the compounds described herein, even though only a single tautomeric form may be represented (e. g. , alkylation of a ring system may result in alkylation at multiple sites, the invention expressly includes all such reaction products). All such isomeric forms of such compounds are expressly included in the present invention. All crystal forms of the compounds described herein are expressly included in the present invention.

The compounds of formula (I) of the invention as described herein in the various embodiments, or a pharmaceutically acceptable salt thereof, or a composition comprising the SCFA compound of formula (I) according to the invention and as described herein, or a pharmaceutically acceptable salt thereof, particularly in a therapeutically effective amount, optionally, together with a pharmaceutically acceptable carrier, is used in the treatment, prevention or attenuation of viral infections and/or virus-induced exacerbations of allergy or autoimmunity

The compounds of formula (I) of the invention as described herein in the various embodiments, or a pharmaceutically acceptable salt thereof, or a composition comprising the SCFA compound of formula (I) according to the invention and as described herein, or a pharmaceutically acceptable salt thereof, particularly in a therapeutically effective amount, optionally, together with a pharmaceutically acceptable carrier, may also be used as an adjuvant for inducing, promoting or enhancing an immune response in a subject treated with an immunogen, for example, an immunogen comprised in a vaccine, particularly a viral vaccine.

In certain embodiments, the present invention relates to a SCFA compound of formula (I) according to the invention and as described herein or to a pharmaceutically acceptable salt thereof, or to a composition comprising the SCFA compound of formula (I) according to the invention and as described herein, or a pharmaceutically acceptable salt thereof, particularly in a therapeutically effective amount, optionally, together with a pharmaceutically acceptable carrier, for use in a method for inducing antigen-specific T cells in a subject, particularly of antigen-specific CD4⁺ T cells or CD8⁺ T cells or both, wherein said SCFA compound of formula (I) or a composition comprising the SCFA compound of formula (I) according to the invention and as described herein is administered to a subject in need thereof.

In one aspect of the invention, the CD8⁺ T cells are memory CD8⁺ T cells.

In another aspect of the invention, said antigen-specific T cells are induced in the airways, particularly in the lung of the subject.

In one embodiment, the SCFA compound of formula (I) or a composition comprising the SCFA compound of formula (I) according to the invention and as described herein in the various embodiments is used for treating a patient suffering from a viral infection, particularly in the airways of a subject.

In one embodiment, the SCFA compound of formula (I) or a composition comprising the SCFA compound of formula (I) according to the invention and as described herein in the various embodiments is used for treating a patient suffering from virus-induced exacerbations of allergic diseases or disorders, particularly in the airways of a subject.

Accordingly, in one embodiment, the present invention relates to a SCFA compound of formula (I) according to the invention and as described herein in the various embodiments or to a pharmaceutically acceptable salt thereof, or to a composition comprising the SCFA compound of formula (I) according to the invention and as described herein, or a pharmaceutically acceptable salt thereof, particularly in a therapeutically effective amount, optionally, together with a pharmaceutically acceptable carrier, for use in the treatment, prevention or attenuation of viral infections and/or virus-induced exacerbations of allergic diseases or disorders, particularly in the airways of a subject, such as asthma, chronic obstructive pulmonary disease and autoimmunity or prevention of a disease or condition, particularly an allergic disease or disorder, or in amelioration of the condition of a subject suffering from such a disease or disorder, including, but without being limited to, an allergic disease or disorder selected from the group consisting of asthma, rhinitis, dermatitis, drug reactions, eosinophilic diseases or disorders, esophageal and gastrointestinal allergy, or a combination thereof.

In a specific embodiment of the invention, said viral infection is, without being limited thereto, selected from the group consisting of Influenza virus, respiratory syncytial virus, human immunodeficiency virus, vaccinia virus, variola virus, dengue virus, coxsackie virus, hepatitis A virus, poliovirus, rhinovirus, Herpes simplex, type 1, Herpes simplex, type 2, Varicella-zoster virus, Epstein-barr virus, Human cytomegalovirus, Human herpesvirus, Hepatitis B virus, Hepatitis C virus, yellow fever virus, dengue virus, West Nile virus, Measles virus, Mumps virus, Parainfluenza virus, Human metapneumovirus, Human papillomavirus, Rabies virus, Rubella virus, Human bocavirus, and Parvovirus B19 infection.

In particular, the SCFA compound of formula (I) or a composition comprising the SCFA compound of formula (I) according to the invention and as described herein in the various

embodiments can also be used for the treatment, prevention or amelioration of virally conferred protection or enhancement of allergy subsequent to infection, or the virally-induced development of immunodeficiency in chronic infection.

Other embodiments of the invention relate to a method for inducing antigen-specific T cells in a subject, particularly of antigen-specific CD4⁺ T cells or CD8⁺ T cells or both, particularly in the airways of said subject, comprising administering to said subject in need thereof a SCFA compound of formula (I) according to the invention and as described herein in the various embodiments or a pharmaceutically acceptable salt thereof, or a composition comprising the SCFA compound of formula (I) according to the invention and as described herein in the various embodiments, or a pharmaceutically acceptable salt thereof, for reducing the amount of T helper 2 (Th2) cell-derived cytokines of a subject treated with said compound, particularly in the airways of said subject and thus for use in the treatment or prevention of a disease or disorder mediated by T helper 2 (Th2) cell-derived cytokines, or for amelioration of the condition of a subject suffering from such a disease or disorder.

Other embodiments of the invention relate to a method for treatment, prevention, or attenuation of viral infections and/or virus-induced exacerbations of allergic diseases or disorders such as asthma, chronic obstructive pulmonary disease and allergy or autoimmunity comprising administering to a subject in need of such a treatment a therapeutically effective amount of a SCFA compound of formula (I) or a composition comprising the compound of formula (I), or a pharmaceutically acceptable salt thereof, particularly in a therapeutically effective amount, optionally, together with a pharmaceutically acceptable carrier.

In a specific embodiment of the invention, said viral infection is, without being limited thereto, selected from the group consisting of Influenza virus, respiratory syncytial virus, human immunodeficiency virus, vaccinia virus, variola virus, dengue virus, coxsackie virus, hepatitis A virus, poliovirus, rhinovirus, Herpes simplex, type 1, Herpes simplex, type 2, Varicella-zoster virus, Epstein-barr virus, Human cytomegalovirus, Human herpesvirus, Hepatitis B virus, Hepatitis C virus, yellow fever virus, dengue virus, West Nile virus, Measles virus, Mumps virus, Parainfluenza virus, Human metapneumovirus, Human papillomavirus, Rabies virus, Rubella virus, Human bocavirus, and Parvovirus B19 infection.

The above compound or composition can also be used in a method for preparing a medicament.

In still another embodiment, the invention relates to a SCFA compound of formula (I) according to the invention and as described herein in the various embodiments or to a pharmaceutically acceptable salt thereof, or to a composition comprising the SCFA

compound of formula (I) according to the invention and as described herein in the various embodiments, or a pharmaceutically acceptable salt thereof, particularly in a therapeutically effective amount, optionally, together with a pharmaceutically acceptable carrier, for use as an adjuvant in inducing, promoting or enhancing an immune response in a subject treated with an immunogen, for example, an immunogen comprised in a vaccine, particularly a viral vaccine.

In one embodiment, the invention relates to a method of inducing, promoting or enhancing an immune response against an immunogen in a subject, comprising: (a) administering an immunogen to a subject in need thereof in an immunogenically effective amount; and (b) administering a SCFA compound of formula (I) according to the invention and as described herein in the various embodiments or a pharmaceutically acceptable salt thereof, or a composition comprising the SCFA compound of formula (I) according to the invention and as described herein in the various embodiments, as an adjuvant to the subject in an adjuvant effective amount.

In one embodiment, the invention relates to the use of a SCFA compound of formula (I) according to the invention and as described herein in the various embodiments or of a pharmaceutically acceptable salt thereof, or to the use of a composition comprising the SCFA compound of formula (I) according to the invention and as described herein in the various embodiments, or a pharmaceutically acceptable salt thereof, as an adjuvant for inducing, promoting or enhancing an immune response against an immunogen.

The above compound or composition can also be used for preparing an adjuvant formulation or a medicament.

In certain embodiments of the invention, said viral vaccines are selected from the group consisting of vaccines towards Influenza virus, respiratory syncytial virus, human immunodeficiency virus, vaccinia virus, variola virus, dengue virus, coxsackie virus, hepatitis A virus, poliovirus, rhinovirus, Herpes simplex, type 1, Herpes simplex, type 2, Varicella-zoster virus, Epstein-barr virus, Human cytomegalovirus, Human herpesvirus, Hepatitis B virus, Hepatitis C virus, yellow fever virus, dengue virus, West Nile virus, Measles virus, Mumps virus, Parainfluenza virus, Human metapneumovirus, Human papillomavirus, Rabies virus, Rubella virus, Human bocavirus, and Parvovirus B19 infections.

Further contemplated are vaccines selected from the group consisting of a diphtheria vaccine, a pertussis vaccine, a tetanus vaccine, a polio vaccine, a hepatitis A vaccine, a hepatitis B vaccine, a rabies vaccine, a measles vaccine, a rubella vaccine, an influenza vaccine, a mumps vaccine, a varicella vaccine, a rota vaccine, a smallpox vaccine, a yellow fever vaccine, a mite-mediated encephalitis vaccine, an Hib vaccine, a typhoid vaccine, a

cholera vaccine, a BCG vaccine, a pneumococcus vaccine and a vaccine against meningitis caused by *Nisseria meningitidis*.

Myeloid precursor cells, but particularly dendritic cells (DCs) are crucial cell types required for inducing inflammatory responses, such as asthma. These cells capture antigens/allergens in the lung and transport them to the draining lymphoid tissue where they activate T cells. These T cells then migrate back to the lung where they are reactivated by lung-resident dendritic cells, and elicit their effector function causing many of the symptoms of asthma (plus list of diseases). Myeloid precursor cells, but particularly dendritic cells thus represent an important rate-limiting step in the development of Th2 and Th17 driven inflammation and modifying their function is a powerful means of regulating inflammation.

It has now been surprisingly found within the scope of the present invention that short chain fatty acids (SCFA) can modulate the number and/or the activation state of myeloid precursor cells, but particularly of dendritic cells (DCs) in an individual, particularly in the airways of an individual, which has major implications on the use and the effectiveness of said compounds in the prevention or amelioration of viral infections, autoimmune diseases, and/or allergic disorders/diseases. It has further been surprisingly found within the scope of the present invention that short chain fatty acids (SCFA) are capable of reducing the release of cytokines from Th2 cells in model animals, but particularly the release of IL-4, IL8 and/or IL-17A. These compounds were further shown to reduce systemic IgE levels in model animals while leaving other important antibody isotypes, including IgG2a, IgG2c and IgA, unaffected. Further, differential cell counts revealed that treatment of model animals with short chain fatty acids also lead to a reduction of eosinophils.

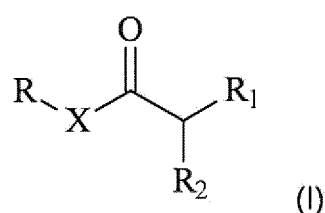
Accordingly, short chain fatty acids of formula (I) according to the present invention as described herein in the various embodiments can be used in human therapy at an early stage for the treatment or, prevention of allergic diseases, or for amelioration of the condition of a subject suffering from such a disease or disorder, particularly of a disease or disorder mediated by T helper 2 (Th2) cell-derived cytokines, including, without being limited to, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, and IL-17A, but particularly of IL-4 and/or IL-8 and/or IL-17A and/or IgE mediated diseases or disorders including, but without being limited to, allergic disorders including autoimmune diseases selected from asthma, rhinitis, dermatitis, drug reactions, esophageal and gastrointestinal allergy.

Short chain fatty acids can further be used in human therapy for the treatment of eosinophilic diseases or disorders comprising nodules, eosinophilia, eosinophilic rheumatism, dermatitis and swelling (NERDS).

In another embodiment, the present invention relates to a SCFA compound of formula (I) according to the invention and as described herein in the various embodiments or to a pharmaceutically acceptable salt thereof, or to a composition comprising the SCFA compound of formula (I) according to the invention and as described herein in the various embodiments, or a pharmaceutically acceptable salt thereof, particularly in a therapeutically effective amount, optionally, together with a pharmaceutically acceptable carrier, for modulating the number and/or the activation state of myeloid precursor cells, but particularly dendritic cells (DCs) in the affected tissue or organ.

In another embodiment, the present invention relates to a SCFA compound of formula (I) according to the invention and as described herein in the various embodiments or to a pharmaceutically acceptable salt thereof, or to a composition comprising the SCFA compound of formula (I) according to the invention and as described herein in the various embodiments, or a pharmaceutically acceptable salt thereof, particularly in a therapeutically effective amount, optionally, together with a pharmaceutically acceptable carrier, for use in a method for the prevention of development of a Th2 induced inflammatory condition in a tissue or organ of a subject, the method comprising administering an effective amount of a compound of formula (I) to the subject, which compound modulates the number and/or the activation state of myeloid precursor cells, but particularly dendritic cells (DCs) in the affected tissue or organ, particularly prior to the activation of a T cell response.

In particular, the compound of formula (I)



is a compound according to the invention and as described herein in the various embodiments, wherein

X represents -O-, -S-, or -NH-, preferably -O-;

R represents hydrogen, alkyl, aryl, arylalkyl, polyalkylene glycol;

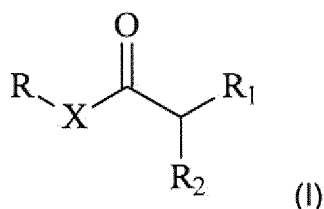
R₁ represents hydrogen, alkyl, hydroxyalkyl, arylalkyl, carboxylic acid;

R₂ represents hydrogen, alkyl, -O-R₃; and

R₃ represents hydrogen, aryl, arylalkyl, hydroxyalkyl-carboxyl;

or a pharmaceutically acceptable salt thereof.

In particular, the compound of formula (I)



is a compound according to the invention and as described herein in the various embodiments, wherein

X represents -O-, -S-, or -NH-, preferably -O-;

R represents hydrogen, alkyl, aryl, arylalkyl, polyalkylene glycol;

R₁ represents hydrogen, alkyl, hydroxyalkyl, arylalkyl, carboxylic acid;

R₂ represents hydrogen, alkyl, -O-R₃; and

R₃ represents hydrogen, aryl, arylalkyl, hydroxyalkyl-carboxyl;

or a pharmaceutically acceptable salt.

In one embodiment, the compound of formula (I) is a compound according to the invention and as described herein in the various embodiments, wherein

X represents -O-, -S-, or -NH-, preferably -O-;

R represents hydrogen, alkyl, aryl, arylalkyl, polyalkylene glycol;

R₁ represents hydrogen, alkyl, hydroxyalkyl, carboxylic acid;

R₂ represents hydrogen, alkyl, -O-R₃; and

R₃ represents hydrogen, aryl, arylalkyl, hydroxyalkyl-carboxyl;

In another embodiment, the compound of formula (I) is a compound according to the invention and as described herein in the various embodiments, wherein

X represents -O-, -S-, or -NH-, preferably -O-;

R represents hydrogen, C₁-C₆ alkyl, unsubstituted or substituted phenyl with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano, C₁-C₄ alkyloxy or trifluoro;

R₁ represents hydrogen, carboxylic acid, C₁-C₆ alkyl, hydroxy-C₁-C₆ alkyl wherein the alkyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of hydroxyl, amino, carboxylic acid, halogen, cyano, or nitro;

R₂ represents hydrogen, C₁-C₆ alkyl, -O-R₃; and

R₃ represents hydrogen, unsubstituted or substituted phenyl with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano, C₁-C₄ alkyloxy or trifluoro, phenyl-C₁-C₆ alkyl wherein the phenyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano, C₁-C₄ alkyloxy or trifluoro, hydroxy-C₁-C₆ alkyl-carboxyl; or pharmaceutically acceptable salts thereof.

In still another embodiment, the compound of formula (I) is a compound according to the invention and as described herein in the various embodiments, wherein

X is -O-,

R is hydrogen;

R₁ represents hydrogen, carboxylic acid, C₁-C₄ alkyl, hydroxy-C₁-C₄ alkyl wherein the alkyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of hydroxyl, amino, or carboxylic acid, preferably hydroxyl and/or carboxylic acid; and

R₂ is hydrogen or C₁-C₄ alkyl; or pharmaceutically acceptable salts thereof.

In one embodiment, the compound of formula (I) is a compound according to the invention and as described herein in the various embodiments, wherein

X is -O-,

R is hydrogen;

R₁ represents hydrogen, carboxylic acid, C₁-C₄ alkyl, hydroxy-C₁-C₄ alkyl wherein the alkyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of hydroxyl, amino or carboxylic acid, preferably hydroxyl and/or carboxylic acid; and

R₂ is -OR₃; and

R₃ represents hydrogen, unsubstituted or substituted phenyl with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano or methoxy, phenyl-C₁-C₄ alkyl wherein the phenyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano or methoxy, hydroxy-C₁-C₃ alkyl-carboxyl; or pharmaceutically acceptable salts thereof.

In one embodiment, the compound of formula (I) is a compound according to the invention and as described herein in the various embodiments, wherein

X is -O-,

R is hydrogen;

R₁ represents hydrogen, carboxylic acid, C₁-C₃ alkyl, hydroxy-C₁-C₃ alkyl wherein the alkyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of hydroxyl and/or carboxylic acid; and R₂ is hydrogen or C₁-C₄ alkyl; or pharmaceutically acceptable salts thereof.

In one embodiment, the compound of formula (I) is a compound according to the invention and as described herein in the various embodiments, wherein

X is -O-,

R is hydrogen;

R₁ represents hydrogen, carboxylic acid, C₁-C₃ alkyl, hydroxy-C₁-C₃ alkyl wherein the alkyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of hydroxyl or carboxylic acid;

R₂ is -OR₃; and

R₃ represents hydrogen, unsubstituted or substituted phenyl with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano or methoxy, phenyl-C₁-C₄ alkyl wherein the phenyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano, or methoxy, hydroxy-C₁-C₃ alkyl-carboxyl; or pharmaceutically acceptable salts thereof.

In one embodiment, the compound of formula (I) is a compound according to the invention and as described herein in the various embodiments, wherein

X is -O-,

R is hydrogen;

R₁ is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, isopropyl, hydroxymethyl, dihydroxymethyl, hydroxyethyldicarboxylic acid, carboxylic acid, methylcarboxylic acid, hydroxymethylcarboxylic, ethylcarboxylic acid; and

R₂ is selected from the group consisting of hydrogen, hydroxyl or methyl; or pharmaceutically acceptable salts thereof.

In one embodiment, the compound of formula (I) is a compound according to the invention and as described herein in the various embodiments, wherein

X is -O-,

R is hydrogen;

R₁ is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, isopropyl;

R₂ is -OR₃; and

R₃ is selected from the group consisting of 1-hydroxyethylcarbonyl, benzyl, nitrophenyl; or pharmaceutically acceptable salts thereof.

In one embodiment, the compound of formula (I) is a compound according to the invention and as described herein in the various embodiments, wherein

X is -O-,

R represents C₁-C₄ alkyl, unsubstituted or substituted phenyl with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano or methoxy, phenyl-C₁-C₄ alkyl wherein the phenyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of halogen, nitro, amino, hydroxyl, cyano or methoxy, polyalkylene glycol;

R₁ is carboxylic acid, C₁-C₄ alkyl or hydroxy-C₁-C₄ alkyl, wherein the alkyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of hydroxyl, amino or carboxylic acid; and

R₂ is hydrogen; or pharmaceutically acceptable salts thereof

In one embodiment, the compound of formula (I) is a compound according to the invention and as described herein in the various embodiments, wherein

X is -O-,

R represents C₁-C₄ alkyl, unsubstituted or substituted phenyl with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano or methoxy, phenyl-C₁-C₄ alkyl wherein the phenyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of halogen, nitro, amino, hydroxyl, cyano or methoxy, polyalkylene glycol;

R₁ is carboxylic acid, C₁-C₃ alkyl or hydroxy-C₁-C₃ alkyl wherein the alkyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of hydroxyl and/or carboxylic acid; and

R₂ is hydrogen; or pharmaceutically acceptable salts thereof.

In one embodiment, the compound of formula (I) is a compound according to the invention and as described herein in the various embodiments, wherein

X is -O-,

R is selected from the group consisting of methyl, ethyl, propyl, benzyl, nitrobenzyl, polyethylene glycol;

R₁ selected from the group consisting of methyl, hydroxymethyl; and

R₂ is hydrogen; or pharmaceutically acceptable salts thereof

In one embodiment, the compound of formula (I) is selected from the group consisting of acetic acid, propionic acid, butyric acid, isobutyric acid, 2-hydroxypropionic acid, dilactic acid, 2-benzyloxypropionic acid, 2-(*p*-nitrophenyl)-oxy-propionic acid, 3-hydroxypropionic acid,

2,3-dihydroxypropionic acid, methyl 3-hydroxypropionate, ethyl 3-hydroxypropionate, propyl 3-hydroxypropionate, benzyl 3-hydroxypropionate, para-nitrophenyl 3-hydroxypropionate, *p*-nitrobenzyl 3-hydroxypropionate, polyethylene glycol 3-hydroxypropionate, methyl propionate, ethyl propionate, propyl propionate, benzyl propionate, *p*-nitrophenyl propionate, *p*-nitrobenzyl propionate, 2-(4-Isobutylphenyl) propionic acid, lactic acid, citric acid, malic acid, malonic acid, succinic acid, and tartaric acid; or pharmaceutical acceptable salts thereof.

In one embodiment, the compound of formula (I) is selected from the group consisting of propionic acid, isobutyric acid, 3-hydroxypropionic acid, 2,3-dihydroxypropionic acid, lactic acid, or citric acid.

In one embodiment, the invention relates to a compound of formula (I) of the invention as disclosed above for use in a method for the prevention of development of a Th2 induced inflammatory condition in a tissue or organ of a subject, the method comprising administering an effective amount of a compound of formula (I) to the subject, which compound modulates the number and/or the activation state of dendritic cells (DCs) in the affected tissue or organ, particularly prior to the activation of a T cell response, with the proviso that

R_1 and R_2 are not hydrogen when X is -O- and R is hydrogen; and/or

R_1 is not alkyl, R_2 is not hydrogen when X is -O- and R is hydrogen; and/or

R_1 and R_2 are not Me when X is NH and R is Ar; and/or

R_1 is not alkyl and R_2 is not hydrogen when X is NH and R is alkyl.

In another embodiment, the present invention relates to a compound of formula (I) according to the invention and as described herein in the various embodiments or to a pharmaceutically acceptable salt thereof, or to a composition comprising the SCFA compound of formula (I) according to the invention and as described herein in the various embodiments, or a pharmaceutically acceptable salt thereof, particularly in a therapeutically effective amount, optionally, together with a pharmaceutically acceptable carrier, for use in human or animal therapy comprising reducing the release of cytokines from Th2 cells and/or of systemic IgE levels, while leaving other antibody isotypes, including IgG2a and IgG2c, unaffected and/or reducing eosinophil infiltration, resulting in treatment or prevention of an associated disease or disorder, or amelioration of the condition of a subject suffering from such a disease or disorder, such as an allergic disease or disorder.

In yet another embodiment, the present invention relates to a compound of formula (I) according to the invention and as described herein in the various embodiments or to a pharmaceutically acceptable salt thereof, or to a composition comprising the SCFA compound of formula (I) according to the invention and as described herein in the various

embodiments, or a pharmaceutically acceptable salt thereof, particularly in a therapeutically effective amount, optionally, together with a pharmaceutically acceptable carrier, for use in human or animal therapy comprising reducing the release of cytokines from Th2 cells and/or of systemic IgE levels, while leaving other antibody isotypes, including IgG2a and IgG2c, unaffected and/or reducing eosinophil infiltration, resulting in treatment or prevention of an associated disease or disorder, or amelioration of the condition of a subject suffering from such a disease or disorder, such as an allergic disease or disorder.

In another certain embodiment, the present invention relates to a SCFA compound of formula (I) according to the invention and as described herein in the various embodiments or to a pharmaceutically acceptable salt thereof, or to a composition comprising the SCFA compound of formula (I) according to the invention and as described herein in the various embodiments, or a pharmaceutically acceptable salt thereof, particularly in a therapeutically effective amount, optionally, together with a pharmaceutically acceptable carrier, for modulating the barrier function and integrity of epithelial cells.

In another certain embodiment, the present invention relates to a SCFA compound of formula (I) according to the invention and as described herein in the various embodiments or to a pharmaceutically acceptable salt thereof, or to a composition comprising the SCFA compound of formula (I) according to the invention and as described herein in the various embodiments, or a pharmaceutically acceptable salt thereof, particularly in a therapeutically effective amount, optionally, together with a pharmaceutically acceptable carrier, for modulating the activity of members of the IL-1 family and the inflammasome.

In another embodiment of the invention, the SCFA compound of formula (I) according to the invention and as described herein in the various embodiments or a pharmaceutically acceptable salt thereof, or a composition comprising the SCFA compound of formula (I) according to the invention and as described herein in the various embodiments, may be used in a method of modulating the number and/or the activation state of myeloid precursor cells, but particularly dendritic cells (DCs) in an individual, particularly in the airways of an individual. Said compounds or compositions can thus be used for an early stage treatment or prevention of allergic diseases, particularly of a disease or disorder mediated by T helper 2 (Th2) cell-derived cytokines, including, without being limited to, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, and IL-17A, but particularly of IL-4 and/or IL-8 and/or IL-17A and/or IgE mediated diseases or disorders including, but without being limited to, allergic disorders including autoimmune diseases selected from asthma, rhinitis, dermatitis, drug reactions, esophageal and gastrointestinal allergy.

Short chain fatty acids can further be used in human therapy for the treatment, particularly for the early stage treatment of eosinophilic diseases or disorders comprising nodules, eosinophilia, eosinophilic rheumatism, dermatitis and swelling (NERDS).

In one embodiment, the present invention relates to a SCFA compound of formula (I) according to the invention and as described herein in the various embodiments or to a pharmaceutically acceptable salt thereof, or to a composition comprising the SCFA compound of formula (I) according to the invention and as described herein in the various embodiments, or a pharmaceutically acceptable salt thereof, particularly in a therapeutically effective amount, optionally, together with a pharmaceutically acceptable carrier, for reducing the circulating levels of immunogen-specific IgE in a subject treated with said compound and exposed to an immunogen, and thus for use in the treatment or prevention of an IgE mediated disease or disorder, or for amelioration of the condition of a subject suffering from such a disease or disorder.

In one embodiment, the present invention relates to a SCFA compound of formula (I) according to the invention and as described herein in the various embodiments or to a pharmaceutically acceptable salt thereof, or to a composition comprising the SCFA compound of formula (I) according to the invention and as described herein in the various embodiments, or a pharmaceutically acceptable salt thereof, particularly in a therapeutically effective amount, optionally, together with a pharmaceutically acceptable carrier, for reducing the number of eosinophils in a subject treated with said compound and exposed to an immunogen, particularly in the airways of said subject, and thus for use in the treatment or prevention of an eosinophilic disease or disorder, or for amelioration of the condition of a subject suffering from such a disease or disorder.

In one embodiment, the disease or disorder is an allergic disease or disorder mediated by T helper 2 (Th2) cell-derived cytokines, including, without however being limited to, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13 or IL-17A, or certain combinations thereof, particularly an IL-4 and/or IL-8, and/or IL-17A mediated disease or disorder, and/or an IgE mediated disease or disorder, particularly a disease or disorder selected from the group consisting of allergic asthma, hay fever, drug allergies, allergic bronchopulmonary aspergillosis (ABPA), esophageal and a gastrointestinal allergy, pemphigus vulgaris, atopic dermatitis, onchocercal dermatitis, viral infections such as Respiratory Syncytial Virus infection or a combination thereof.

In one embodiment, the asthma is steroid resistant asthma, neutrophilic asthma or non-allergic asthma

In one embodiment, the allergic disease or disorder is an eosinophilic disease or disorder, particularly a disease or disorder selected from the group consisting of nodules, eosinophilia, eosinophilic rheumatism, dermatitis and swelling (NERDS).

In another embodiment, the allergic disease or disorder is an IgE-mediated disease or disorder, particularly a disease or disorder selected from the group consisting of urticaria, eczema conjunctivitis, rhinorrhea, rhinitis, particularly allergic rhinitis, gastroenteritis, or a combination thereof.

In still another embodiment, an IgE-mediated disease or disorder comprises myeloma, multiple myeloma, Hodgkin's disease, Hyper-IgE syndrome, Wiskott-Aldrich syndrome, Chronic Obstructive Pulmonary Disease and exacerbations of Chronic Obstructive Pulmonary Disease or a combination thereof.

In certain embodiments, the invention relate to a method for modulating the number and/or the activation state of myeloid precursor cells, but particularly dendritic cells (DCs in the affected tissue or organ, said method comprising applying at an early stage to a subject in need of such a treatment a therapeutically effective amount of a SCFA compound of formula (I) or of a composition comprising the compound of formula (I), or a pharmaceutically acceptable salt thereof, particularly in a therapeutically effective amount, optionally, together with a pharmaceutically acceptable carrier, particularly prior to the activation of a T cell response.

In particular, the invention relates to a method for the prevention of development of a Th2 induced inflammatory condition in a tissue or organ of a subject, the method comprising administering an effective amount of a compound of formula (I) to the subject, which compound modulates the number and/or the activation state of myeloid precursor cells, but particularly dendritic cells (DCs) in the affected tissue or organ, said method comprising applying at an early stage to a subject in need of such a treatment a therapeutically effective amount of a SCFA compound of formula (I) or of a composition comprising the compound of formula (I), or a pharmaceutically acceptable salt thereof, particularly in a therapeutically effective amount, optionally, together with a pharmaceutically acceptable carrier, particularly prior to the activation of a T cell response.

Other embodiments of the invention relate to a method for the treatment or prevention of a disease or disorder mediated by T helper 2 (Th2) cell-derived cytokines, including, without however being limited to, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13 or IL-17A, or certain combinations thereof, particularly an IL-4 and/or IL-8, and/or IL-17A mediated disease or disorder, and/or an IgE mediated disease or disorder and/or an eosinophilic disease or disorder, or for amelioration of the condition of a subject suffering from such a disease or

disorder, said method comprising applying to a subject in need of such a treatment a therapeutically effective amount of a SCFA compound of formula (I) or of a composition comprising the compound of formula (I), or a pharmaceutically acceptable salt thereof, particularly in a therapeutically effective amount, optionally, together with a pharmaceutically acceptable carrier.

In one embodiment, the invention relates to a method for selectively controlling, particularly for selectively reducing, allergen-specific IgE antibody levels in a subject suffering from IgE-mediated disease or disorder comprising applying to a subject in need of such a treatment a therapeutically effective amount of a SCFA compound of formula (I) or of a composition comprising the compound of formula (I), or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount, optionally, together with a pharmaceutically acceptable carrier. In a specific embodiment, such a treatment does not affect or increases IgG levels, particularly IgG2a, IgG2c levels, and/or IgA levels, in the treated subject.

In one embodiment, the invention relates to a method for reducing the release of IL-4, and/or IL-8, and/or IL-17A, from Th2 cells in a subject suffering from an IL-4, and/or IL-8, and/or IL-17A mediated disease or disorder comprising applying to a subject in need of such a treatment a therapeutically effective amount of a SCFA compound of formula (I) or of a composition comprising the compound of formula (I), or a pharmaceutically acceptable salt thereof, particularly in a therapeutically effective amount, optionally, together with a pharmaceutically acceptable carrier. In a specific embodiment, such a treatment also reduces the allergen-specific IgE antibody levels in a subject, but does not affect or increases IgG levels, particularly IgG2a, IgG2c levels, and/or IgA levels, in the treated subject.

In another embodiment, the invention relates to a method for use in the treatment or prevention of an allergic disease or disorder, or for amelioration of the condition of a subject suffering from an allergic disease or disorder, including, but without being limited to, an allergic disease or disorder selected from the group consisting of asthma, rhinitis, dermatitis, drug reactions, eosinophilic diseases or disorders, esophageal and gastrointestinal allergy, or a combination thereof comprising applying to a subject in need of such a treatment a therapeutically effective amount of a SCFA compound of formula (I) or of a composition comprising the compound of formula (I), or a pharmaceutically acceptable salt thereof, particularly in a therapeutically effective amount, optionally, together with a pharmaceutically acceptable carrier.

In one embodiment, the allergic disease or disorder is an IL-4- and/or IL-8- and/or IL-17A-mediated disease or disorder and/or an IgE mediated disease or disorder, particularly a

disease or disorder selected from the group consisting of allergic asthma, hay fever, drug allergies, allergic bronchopulmonary aspergillosis (ABPA), esophageal and a gastrointestinal allergy, pemphigus vulgaris, atopic dermatitis, onchocercal dermatitis, or a combination thereof.

In one embodiment, the allergic disease or disorder is an eosinophilic disease or disorder, particularly a disease or disorder selected from the group consisting of nodules, eosinophilia, eosinophilic rheumatism, dermatitis and swelling (NERDS).

In another embodiment, the allergic disease or disorder is an IgE-mediated disease or disorder, particularly a disease or disorder selected from the group consisting of urticaria, eczema conjunctivitis, rhinorrhea, rhinitis, particularly allergic rhinitis, gastroenteritis, or a combination thereof.

In still another embodiment, an IgE-mediated disease or disorder comprises myeloma, multiple myeloma, Hodgkin's disease, Hyper-IgE syndrome, Wiskott-Aldrich syndrome, or a combination thereof.

In certain embodiments, the present invention provides a method for the manufacture of the compositions according to the invention and as described herein in the various embodiments comprising one or more SCFA compound of formula (I) according to the invention and as described herein in the various embodiments as active ingredients which process comprises mixing one or more SCFA compounds of formula (I) with an inert carrier or excipient that is acceptable to the target organism that is in need of the treatment.

Definition

The technical terms and expressions used within the scope of this application are generally to be given the meaning commonly applied to them in the pertinent art if not otherwise indicated herein below.

As used in this specification and 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 compound" includes one or more compounds.

"Alkyl" as such means a straight-chained or branched saturated aliphatic hydrocarbon having from 1 to 10 carbon atoms, wherein the alkyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of hydroxyl, amino, carboxylic acid, halogen, cyano, or nitro. Preferred are C₁-C₆ alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl (amyl), 2-pentyl (sec-pentyl), 3-pentyl, 2-methylbutyl, 3-methylbutyl (= iso-pentyl or iso-amyl), 3-methylbut-2-yl, 2-methylbut-2-yl, 2,2-dimethylpropyl (= neopentyl), n-hexyl, iso-hexyl, sec-

hexyl, tert.-hexyl and the like. Most preferred are C₁-C₄ alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl.

"Hydroxyalkyl" stands for one of the above-defined alkyl groups wherein at least one hydrogen atom is replaced by a hydroxyl group and wherein the hydroxyalkyl group may be unsubstituted or substituted with one or more, same or different substituents selected from the group consisting of hydroxyl, amino, carboxylic acid, halogen, cyano, or nitro. Typical representatives are -CH₂OH, -CH₂CH₂OH, -CH(OH)-CH₃, -CH(OH)CH₂CH₃, CH₂CH(CH₂CH₂OH)CH₂CH₃, etc..

"Aryl" means a monovalent, monocyclic, bicyclic or tricyclic, aromatic carbocyclic hydrocarbon radical, preferably a 6-14 member aromatic ring system. Preferred aryl groups include, but are not limited to phenyl, naphthyl, phenanthrenyl, and anthracenyl, wherein the aryl group may be unsubstituted or substituted with one or more, same or different substituents selected from the group consisting of halogen; alkyl; alkyloxy; cyano, trifluoro, nitro, amino, hydroxyl.

"Alkoxy" means -O-alkyl, wherein alkyl has the meaning given above.

"Halogen" means fluorine, chlorine, bromine, or iodine, preferably fluorine, chlorine or iodine.

"Polyalkylene glycol" means a moiety that comprises at least two alkylene glycol units such as -O-alkyl-O-alkyl-O- moiety wherein alkyl have the meaning given above. The polyalkylene glycol moiety may be solely comprised of polyalkylene glycol, or may be part of a larger structure, such as polyoxyalkylated glycerol and other polyoxyalkylated polyols such as polyoxyethylated sorbitol or polyoxyethylated glucose. The number of alkylene units may vary and is greater than 1. Preferred, polyalkylene glycol are polyethylene glycol (PEG) or polypropylene glycol (PPG). Most preferred polyalkylene glycol are PEG wherein the number of ethylene units may vary from 8 to 150.000 or more, particularly from 10 to 80.000, more particularly from 20 to 10.000.

The term "propionate" refers to the pharmaceutically acceptable salt of propionic acid such as, for example, the sodium salt of propionic acid.

The term "pharmaceutically acceptable salts" include salts of acidic or basic groups present in compounds of the invention. Pharmaceutically acceptable acid addition salts include, but are not limited to, hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate,

benzensulfonate, p-toluenesulfonate and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Certain compounds of the invention can form pharmaceutically acceptable salts with various amino acids. Suitable base salts include, but are not limited to, aluminum, calcium, lithium, magnesium, potassium, sodium, zinc, and diethanolamine salts.

The terms "treatment", "treating" and the like are used herein to generally mean obtaining a desired pharmacological and/or physiological 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 partially or completely curing a disease and/or adverse effect attributed to the disease. The term "treatment" as used herein covers any treatment of a disease in a subject and includes: (a) preventing a disease related to an undesired immune response from occurring in a subject which may be predisposed to the disease; (b) inhibiting the disease, i.e. arresting its development; or (c) relieving the disease, i.e. causing regression of the disease.

A "patient" or "subject" for the purposes of the present invention is used interchangeably and meant to include both humans and other animals, particularly mammals, and other organisms. Thus, the methods are applicable to both human therapy and veterinary applications. In the preferred embodiment the patient or subject is a mammal, and in the most preferred embodiment the patient or subject is a human.

The term "attenuation" as used herein refers to reduction of a viral infection in a subject or in a tissue of a subject, particularly in lung tissue of a subject, i.e. reduction or clearance of the amount of virus or viral load. The particular degree or level of the reduction or clearance is at least 15%, 25%, 35%, 50%, 65%, 75%, 80%, 85%, 90%, 95%, 98% or more.

The term "adjuvant" as used herein refers to a substance that increases or promotes the ability of an immunogen (i.e., antigen) to stimulate an immune response against the immunogen in the subject subjected to the immunogen. In particular embodiments, the adjuvant increases the immune response against the immunogen by at least 2, 3, 4, 5, 10, 15, 20, 30, 40, 50, 60, 75, 100, 150, 500, 1000-fold or more. In other embodiments, the adjuvant reduces the amount of immunogen required to achieve a particular level of immune response (cellular and/or humoral and/or mucosal), e.g., a reduction of at least 15%, 25%, 35%, 50%, 65%, 75%, 80%, 85%, 90%, 95%, 98% or more. An adjuvant can further be a substance that prolongs the time over which an immune response, optionally protective immune response, is sustained (e.g., by at least a 2-fold, 3-fold, 5-fold, 10-fold, 20-fold longer time period or more).

The terms "myeloid precursors", "myeloid lineage" or "myeloid cells" refer all to multipotent stem cells as one of two lineages of hematopoietic cells, which are able to develop into

monocytes, macrophages, dendritic cells, neutrophils, eosinophils, basophils, megacaryocytes, platelets or erythrocytes.

A "modulating compound" refers to a compound as described herein in the various embodiments, which may either up-regulate (e.g., activate or stimulate), down-regulate (e.g., inhibit or suppress) or otherwise change a functional property or biological activity of a target molecule or gene. A modulating compound may act to modulate a target molecule or a gene encoding said target molecule either directly or indirectly. In certain embodiments, a modulating compound may be an activating compound or an-inhibiting compound.

The "modulation of a Th2 or Th2-like immune response towards a Th1 immune response" refers to a change from a "humoral immune response" executed mainly by antibodies, B cells, plasma cells and/or memory B cells towards a "cellular immune response, executed mainly by CD8+ T cells and phagocytes, e.g. macrophages. This modulation implements also a change in the cytokine composition which is characteristic for each of the two distinct T helper cell mechanisms. A Th2 or Th2-like immune response is mediated by IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, and/or IL-17A, particularly IL-4 and/or IL-8 and/or IL-17A, whereas a Th1 immune response is mediated by interferon-gamma (IFN-gamma), IL-2, and tumor necrosis factor-alpha (TNF-alpha). Further "modulation" means particularly prior to the activation of a T cell response.

The expressions "pharmaceutical composition" and "therapeutical composition" are used herein interchangeably in the widest sense. They are meant to refer, for the purposes of the present invention, to a therapeutically effective amount of the active ingredient, i.e. the SCFA compound of formula (I) or a pharmaceutically acceptable salt thereof, optionally, together with a pharmaceutically acceptable carrier or diluent.

It embraces compositions that are suitable for the curative treatment, the control, the amelioration, an improvement of the condition or the prevention of a disease or disorder in a human being or a non-human animal. Thus, it embraces pharmaceutical compositions for the use in the area of human or veterinary medicine. Such a "therapeutic composition" is characterized in that it embraces at least one SCFA compound of formula (I) compound or a physiologically acceptable salt thereof, and optionally a carrier or excipient whereby the salt and the carrier and excipient are tolerated by the target organism that is treated therewith.

A "therapeutically effective amount" refers to that amount which provides a therapeutic effect for a given condition and administration regimen. In particular, "therapeutically effective amount" means an amount that is effective to prevent, alleviate or ameliorate symptoms of the disease or prolong the survival of the subject being treated, which may be

a human or non-human animal. Determination of a therapeutically effective amount is within the skill of the person skilled in the art.

The therapeutically effective amount or dosage of a compound according to this invention can vary within wide limits and may be determined in a manner known in the relevant art. The dosage can vary within wide limits and will, of course, have to be adjusted to the individual requirements in each particular case.

An "immunogenically effective amount" refers to that amount of an immunogen which provides an active immune response (cellular and/or humoral) in a subject. In some embodiments of the invention, said immune response is sufficient to provide a protective effect, which does not need to be complete or permanent. Determination of an immunogenically effective amount is within the skill of the person skilled in the art.

An "adjuvant effective amount" refers to that amount of an adjuvant that enhances or stimulates the active immune response (cellular and/or humoral or optionally an active mucosal immune response) provided by the immunogen in a subject when subjected to the immunogen.

In the context of protective immune responses, the term "adjuvant effective amount" refers to an amount of the adjuvant that is needed to accelerate the induction of the immune response in the host and/or may be sufficient to reduce the need for booster immunizations to achieve protection.

In the context of prolongation of an immune response, the term "adjuvant effective amount" refers to an amount that prolongs the time period over which an immune response, optionally protective immune response, is sustained.

Determination of an adjuvant effective amount in the above addressed contexts is within the skill of the person skilled in the art.

The SCFAs of formula (I) may be provided as such or in form of a composition, particularly a pharmaceutical composition. Said compositions may comprise additional medicinal agents, pharmaceutical agents, carriers, buffers, adjuvants, dispersing agents, diluents, and the like depending on the intended use and application.

Administration of the suitable (pharmaceutical) compositions containing the active ingredient according to the invention and as disclosed herein, may be effected by different ways known to a person skilled in the art, e.g., by parenteral, subcutaneous, intraperitoneal, topical, transmucosal, transdermal, intrabronchial, intrapulmonary and intranasal, intraventricular, intraarticular, intrathecal, intravaginal, intratracheal, administration and, if desired for local treatment, intralesional administration. Parenteral administrations include intraperitoneal, intramuscular, intradermal, subcutaneous, intravenous or intraarterial

administration. The compositions of the invention may also be administered directly to the target site, e.g., by biolistic delivery to an external or internal target site, like a specifically effected organ or a tumor.

Broadly, the present invention provides an oral nutritional composition, for oral consumption and optionally for enteral adsorption, wherein the nutritional composition includes the compounds of the present invention.

If the nutritional compositions are formulated to be administered orally, the compositions may be a liquid oral nutritional supplement (e.g., incomplete feeding) or a complete feeding. In this manner, the nutritional compositions may be administered in any known form including, for example, tablets, capsules, liquids, chewables, soft gels, sachets, powders, syrups, liquid suspensions, emulsions and solutions in convenient dosage forms.

"A nutritional composition" may be a food product intended for human consumption, for example, a beverage, a drink, a bar, a snack, an ice cream, a dairy product, for example a chilled or a shelf-stable dairy product, a fermented dairy product, a drink, for example a milk-based drink, an infant formula, a growing-up milk, a confectionery product, a chocolate, a cereal product such as a breakfast cereal, a sauce, a soup, an instant drink, a frozen product intended for consumption after heating in a microwave or an oven, a ready-to-eat product, a fast food or a nutritional formula.

A nutritional formula encompasses any nutritionally complete or supplementary formulation (a nutritional supplement, for example). As used herein, "nutritionally complete" are preferably nutritional products that contain sufficient types and levels of macronutrients (protein, fats and carbohydrates) and micronutrients to be sufficient to be a sole source of nutrition for the subject to which it is being administered to. Patients can receive 100% of their nutritional requirements from such complete nutritional compositions. According to one embodiment, the nutritional formula is a supplementary formulation providing supplementary nutrition. A "supplementary formula" may not be nutritionally complete, but preferably contains specific nutrients that are supportive, for example in combination with physical exercise, with further of the beneficial effects of the invention, and/or which address specific or additional needs of the subject.

The nutritional formula may be a generally applicable nutritional formula, for example adapted to subjects of a specific age, for example a formula for children, but it may also be a formula for elderly patients, for intensive care patients, or a specially adapted formula for patients suffering from a specific disease, for example. Any nutritional formula may be

reconstitutable, that is, present in a substantially dried, for example powdered form, or ready-to-drink, in the form of liquid formulas, for example.

All the details are enclosed in WO2012022947, which is incorporated herein by reference.

The compounds of the present invention and the pharmaceutical compositions containing said compounds, may be administered orally, and thus be formulated in a form suitable for oral administration, i.e. as a solid or a liquid preparation. Suitable solid oral formulations include tablets, capsules, pills, granules, pellets and the like. Suitable liquid oral formulations include solutions, suspensions, dispersions, emulsions, oils and the like. If formulated in form of a capsule, the compositions of the present invention comprise, in addition to the active compound and the inert carrier or diluent, a hard gelating capsule.

The compounds of the present invention and the pharmaceutical compositions containing said compounds may be further administered intranasally, i.e. by inhalation and thus may be formulated in a form suitable for intranasal administration, i.e. as an aerosol or a liquid preparation.

The compounds of the present invention may also, for example, be formulated as suppositories, containing conventional suppository bases for use in human or veterinary medicine or as pessaries, for example, containing conventional pessary bases.

Examples of suitable pharmaceutical carriers, excipients and/or diluents are well known in the art and include, but are not limited to, a gum, a starch (e.g. corn starch, pregeletanized starch), a sugar (e.g., lactose, mannitol, sucrose, dextrose), a cellulosic material (e.g. microcrystalline cellulose), an acrylate (e.g. polymethylacrylate), calcium carbonate, magnesium oxide, talc, or mixtures thereof.

Pharmaceutically acceptable carriers for liquid formulations are aqueous or non-aqueous solutions, suspensions, emulsions or oils. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, and injectable organic esters such as ethyl oleate. Examples of oils are those of animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, olive oil, sunflower oil, fish-liver oil, another marine oil, or a lipid from milk or eggs.

Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media such as phosphate buffered saline solutions, water, emulsions, such as oil/water emulsions, various types of wetting agents, sterile solutions etc. Compositions comprising such carriers can be formulated by well known conventional methods. Suitable carriers may comprise any material which, when combined with the biologically active compound of the invention, retains the biological activity.

Preparations for parenteral administration may include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles may include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles may include fluid and nutrient replenishes, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives may also be present including, for example, antimicrobials, anti-oxidants, chelating agents, and inert gases and the like. In addition, the pharmaceutical composition of the present invention might comprise proteinaceous carriers, like, e.g., serum albumin or immunoglobulin, preferably of human origin.

The compounds of the present invention and as described herein in the various embodiments and the pharmaceutical compositions containing said compounds may be administered topically to body surfaces and thus be formulated in a form suitable for topical administration. Suitable topical formulations include gels, ointments, creams, lotions, drops and the like. For topical administration, the compound of formula (I) is prepared and applied as a solution, suspension, or emulsion in a physiologically acceptable diluent with or without a pharmaceutical carrier.

The pharmaceutical compositions provided herein may also be administered as controlled-release compositions, i.e. compositions in which the active ingredient is released over a period of time after administration. Controlled- or sustained-release compositions include formulation in lipophilic depots (e.g. fatty acids, waxes, oils). In another embodiment, the composition is an immediate-release composition, i.e. a composition in which all the active ingredient is released immediately after administration.

Further, the compound of formula (I) according to the invention and as described herein in the various embodiments may or a composition comprising said compound may be administered admixed to food, functional food, drinks, medicinal food.

Further examples for suitable formulations are provided in WO 2006/085983, the entire contents of which are incorporated by reference herein. For example, the SCFAs of the present invention may be provided as liposomal formulations. The technology for forming liposomal suspensions is well known in the art. When the adjuvant is an aqueous-soluble salt, using conventional liposome technology, the same can be incorporated into lipid vesicles. The lipid layer employed can be of any conventional composition and can either contain cholesterol or can be cholesterol-free. The liposomes can be reduced in size, as

through the use of standard sonication and homogenization techniques. Liposomal formulations containing the adjuvant can be lyophilized, alone or with immunogen, to produce a lyophilizate which can be reconstituted with a pharmaceutically acceptable carrier, such as water, to regenerate a liposomal suspension. These pharmaceutical compositions can be administered to the subject at a suitable dose. The dosage regimen will be determined by the attending physician and clinical factors. As is well known in the medical arts, dosages for any one patient depend upon many factors, including the patient's size, body surface area, age, the particular compound to be administered, sex, time and route of administration, general health, and other drugs being administered concurrently.

The SCFA compounds of formula (I) and as described herein in the various embodiments may be used in human and veterinary medicine for treating humans and animals, including avians, non-human primates, dogs, cats, pigs, goats, sheep, cattle, horses, mice, rats and rabbits.

Suitable dosages of the SCFAs according to the invention and as described herein in the various embodiments will vary depending upon the condition, age and species of the subject, and can be readily determined by those skilled in the art. The total daily dosages of the compound of formula (I) employed in both veterinary and human medicine will suitably be in the range 0,01-2000 mg/kg body-weight, preferably from 0,1-1000 mg/kg body-weight, preferably from 1-100 mg/kg and these may be administered as single or divided doses, and in addition, the upper limit can also be exceeded when this is found to be indicated. Such dosage will be adjusted to the individual requirements in each particular case including the specific compound(s) being administered, the route of administration, the condition being treated, as well as the patient being treated. However, the compounds can also be administered as depot preparations (implants, slow-release formulations, etc.) weekly, monthly or at even longer intervals. In such cases the dosage will be much higher than the daily one and has to be adapted to the administration form, the body weight and the concrete indication. The appropriate dosage can be determined by conducting conventional model tests, preferably animal models. In general, in the case of oral or parenteral administration to adult humans weighing approximately 70 kg, a daily dosage of about 10 mg to about 10.000 mg, preferably from about 200 mg to about 1.000 mg, should be appropriate, although the upper limit may be exceeded when indicated. The daily dosage can be administered as a single dose or in divided doses, or for parenteral administration; it may be given as continuous infusion.

An effective dose of active ingredient(s) depends at least on the nature of the condition being treated, toxicity, whether the compound(s) is being used prophylactically (lower doses) or against an active infection or condition, the method of delivery, and the

pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.05 to about 30 mg/kg body weight per day. For example, for topical delivery the daily candidate dose for an adult human of approximately 70 kg body weight will range from about 1 mg to about 500 mg, generally between about 5 mg and about 40 mg, and may take the form of single or multiple doses or administration sites.

If used as an adjuvant, the SCFA compound of the invention and as described herein in the various embodiments and/or the immunogen may be given in form of a single or multiple (i.e., booster) dosage.

The immunogen and adjuvant can be co-administered concurrently (e.g., within hours of each other) in the same or different composition and, in the latter case, by the same or different route. Alternatively, the adjuvant can be administered prior to or after administration of the immunogen (e.g., about 6, 12, 24, 36, 48, 72, 96 or 120 hours or more before or after administration of the immunogen).

Further, if used as an adjuvant, the SCFA compound of the invention and as described herein in the various embodiments may administered mixed with immunogen, such as viral antigens, to enhance the immune response elicited against these antigens or alternatively the compound may be chemically coupled to the immunogen directly or in the case of particles (e.g. nanoparticles or virus-like particles (VLP)) the compound could be bound to the surface or encapsulated within said particles.

Furthermore, it is envisaged that the pharmaceutical composition of the invention might comprise further biologically active agents, depending on the intended use of the pharmaceutical composition. These further biologically active agents may be e.g. antibodies, antibody fragments, hormones, growth factors, enzymes, binding molecules, cytokines, chemokines, nucleic acid molecules and drugs. In a preferred embodiment, the pharmaceutical composition of the present invention is to be co-administered with other known immunosuppressive drug or treatments. Such immunosuppressive drugs may be selected from the group consisting of glucocorticoids, cytostatics such as methotrexate, myophenolate or azathioprine, antibodies such as T cell receptor directed antibodies or IL-4 receptor directed antibodies and drugs acting on immunophilins such as cyclosporine, tacrolimus, sirolimus and the like.

The invention present invention further contemplates the use of a SCFA compound of formula (I) according to the invention and as described herein in the various embodiments or a pharmaceutically acceptable salt thereof, or of a composition comprising the SCFA compound of formula (I) according to the invention and as described herein in the various

embodiments, or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount, optionally, together with a pharmaceutically acceptable carrier, for use as an adjuvant in promoting or enhancing an immune response in a subject in need thereof.

The immunogen can be any immunogen known in the art and can be administered in any suitable form as described, for example, in WO 2006/085983, the entire contents of which are incorporated by reference herein.

For example, the immunogen can be in the form of a live, attenuated live, or killed (i.e., inactivated) organism (e.g., a bacterium or protozoan) or virus, or an extract or toxoid thereof. In other embodiments, the immunogen can be provided as an isolated component (e.g., a polypeptide or a peptide [e.g., from about 6 to 20 or 8 to 12 amino acids in length]). Further, the immunogen can be administered per se or can be expressed from a nucleic acid that is administered to the host and the immunogen expressed therefrom. The immunogen can comprise B cell and/or T cell epitopes as are known in the art. The immunogen can further be soluble or particulate (e.g., microspheres).

In the alternative, the immunogen can be present in the organism. For example, in the case of a chronic or latent infection in the subject, the subject fails to mount a sufficient immune response against the antigen. The adjuvants of the invention can be administered to the subject to induce an immune response against the antigen already present in the subject as a result of the infection.

The immunogen can be an immunogen from an infectious agent, a cancer immunogen, an allergic reaction immunogen (i.e., an allergen), a transplantation immunogen, an autoantigen, and the like as are known in the art such as those described in WO 2006/085983.

The cancer that may be treated or immunized against (i.e., prophylactic treatment) by administration to a subject of the adjuvant of the invention can be a cancer selected from the group consisting of B cell lymphoma, T cell lymphoma, myeloma, leukemia, hematopoietic neoplasias, thymoma, lymphoma, sarcoma, lung cancer, liver cancer, non-Hodgkins lymphoma, Hodgkins lymphoma, uterine cancer, adenocarcinoma, breast cancer, pancreatic cancer, colon cancer, lung cancer, renal cancer, bladder cancer, liver cancer, prostate cancer, ovarian cancer, primary or metastatic melanoma, squamous cell carcinoma, basal cell carcinoma, brain cancer, angiosarcoma, hemangiosarcoma, head and neck carcinoma, thyroid carcinoma, soft tissue sarcoma, bone sarcoma, testicular cancer, uterine cancer, cervical cancer, gastrointestinal cancer, and any other cancer now known or later identified (see, e.g., Rosenberg (1996) *Ann. Rev. Med.* 47:481-491, the entire contents of which are incorporated by reference herein).

Further immunogens contemplated within the scope of the present invention are infectious agent immunogens that can include any immunogen suitable for protecting a subject against an infectious disease, including but not limited to microbial, bacterial, protozoal, parasitic and viral diseases.

Examples of such infectious agent immunogens are disclosed in WO 2006/085983 and can include, but are not limited to, immunogens from Hepadnaviridae including hepatitis A, B, C, D, E, F, G, etc.; Flaviviridae including human hepatitis C virus (HCV), yellow fever virus and dengue viruses; Retroviridae including human immunodeficiency viruses (HIV), simian immunodeficiency virus (SIV), and human T lymphotropic viruses (HTLV1 and HTLV2); Herpesviridae including herpes simplex viruses (HSV-1 and HSV-2), Epstein Barr virus (EBV), cytomegalovirus, varicella-zoster virus (VZV), human herpes virus 6 (HHV-6) human herpes virus 8 (HHV-8), and herpes B virus; Papovaviridae including human papilloma viruses; Rhabdoviridae including rabies virus; Paramyxoviridae including respiratory syncytial virus; Reoviridae including rotaviruses; Bunyaviridae including hantaviruses; Filoviridae including Ebola virus; Adenoviridae; Parvoviridae including parvovirus B19; Arenaviridae including Lassa virus; Orthomyxoviridae including influenza viruses; Poxviridae including Orf virus, molluscum contagiosum virus, smallpox virus and Monkey pox virus; Togaviridae including Venezuelan equine encephalitis virus; Coronaviridae including corona viruses such as the severe acute respiratory syndrome (SARS) virus; and Picornaviridae including polioviruses; rhinoviruses; orbiviruses; picodnaviruses; encephalomyocarditis virus (EMV); Parainfluenza viruses, adenoviruses, Coxsackieviruses, Echoviruses, Rubeola virus, Rubella virus, human papillomaviruses, Canine distemper virus, Canine contagious hepatitis virus, Feline calicivirus, Feline rhinotracheitis virus, TGE virus (swine), Foot and mouth disease virus, simian virus 5, human parainfluenza virus type 2, human metapneumovirus, enteroviruses, and any other pathogenic virus now known or later identified (see, e.g., Fundamental Virology, Fields et al., Eds., 3rd ed., Lippincott-Raven, New York, 1996, the entire contents of which are incorporated by reference herein for the teachings of pathogenic viruses).

Further, the immunogen may be an orthomyxovirus immunogen (e.g., an influenza virus immunogen, such as the influenza virus hemagglutinin (HA) surface protein, influenza neuraminidase protein, the influenza virus nucleoprotein (NP) antigen or inactivated influenza virions, or an equine influenza virus immunogen), or a lentivirus immunogen (e.g., an equine infectious anemia virus immunogen, a SIV immunogen, or a HIV immunogen, such as, e.g., HIV or SIV gp120, gp160, gp41, or matrix/capsid protein, or the gag, pol or env gene products). The immunogen may also be an arenavirus immunogen (e.g., Lassa fever virus immunogen, such as the Lassa fever virus nucleocapsid protein gene and the

Lassa fever envelope glycoprotein gene), a Picornavirus immunogen (e.g., a Foot and Mouth Disease virus immunogen), a poxvirus immunogen (e.g., a vaccinia immunogen, such as the vaccinia L1 or L8 genes), an Orbivirus immunogen (e.g., an African horse sickness virus immunogen), a flavivirus immunogen (e.g., a yellow fever virus immunogen, a West Nile virus immunogen, or a Japanese encephalitis virus immunogen), a filovirus immunogen (e.g., an Ebola virus immunogen, or a Marburg virus immunogen, such as NP and GP genes), a bunyavirus immunogen (e.g., RVFV, CCHF, and SFS immunogens), a norovirus immunogen (e.g., a Norwalk virus immunogen), or a coronavirus immunogen (e.g., an infectious human coronavirus immunogen, such as the human coronavirus envelope glycoprotein gene, or a porcine transmissible gastroenteritis virus immunogen, or an avian infectious bronchitis virus immunogen). The immunogen may further be a polio antigen, herpes antigen (e.g., CMV, EBV, HSV antigens) mumps antigen, measles antigen, rubella antigen, diphtheria toxin or other diphtheria antigen, pertussis antigen, hepatitis (e.g., hepatitis A or hepatitis B) antigen (e.g., HBsAg, HBcAg, HBeAg), or any other vaccine immunogen known in the art.

In particular, the immunogen may be from an influenza virus, respiratory syncytial virus, human immunodeficiency virus, vaccinia virus, variola virus, dengue virus, coxsackie virus, hepatitis A virus, poliovirus, rhinovirus, Herpes simplex, type 1, Herpes simplex, type 2, Varicella-zoster virus, Epstein-barr virus, Human cytomegalovirus, Human herpesvirus, Hepatitis B virus, Hepatitis C virus, yellow fever virus, dengue virus, West Nile virus, Measles virus, Mumps virus, Parainfluenza virus, Human metapneumovirus, Human papillomavirus, Rabies virus, Rubella virus, Human bocavirus, Parvovirus B19.

The immunogen can further be an immunogen from a pathogenic microorganism, including, without being limited to, Rickettsia, Chlamydia, Mycobacteria, Clostridia, Corynebacteria, Mycoplasma, Ureaplasma, Legionella, Shigella, Salmonella, pathogenic Escherichia coli species, Bordetella, Neisseria, Treponema, Bacillus, Haemophilus, Moraxella, Vibrio, Staphylococcus spp., Streptococcus spp., Campylobacter spp., Borrelia spp., Leptospira spp., Erlichia spp., Klebsiella spp., Pseudomonas spp., Helicobacter spp., and any other pathogenic microorganism now known or later identified (see, e.g., Microbiology, Davis et al, Eds., 4th ed., Lippincott, New York, 1990, the entire contents of which are incorporated herein by reference for the teachings of pathogenic microorganisms).

The immunogen can further be an immunogen from a pathogenic protozoa or a pathogenic yeast and fungi.

The immunogen can also be an immunogen from chronic or latent infective agents, which typically persist because they fail to elicit a strong immune response in the subject.

Illustrative latent or chronic infective agents include, but are not limited to, hepatitis B, hepatitis C, Epstein-Barr Virus, herpes viruses, human immunodeficiency virus, and human papilloma viruses.

Immunogens that are allergens are also contemplated by the present invention, which can include but are not limited to, environmental allergens such as dust mite allergens; plant allergens such as pollen, including ragweed pollen; insect allergens such as bee and ant venom; and animal allergens such as cat dander, dog dander and animal saliva allergens.

Accordingly, the compounds of formula (I) according to the invention and as described herein in the various embodiments may be used for allergy immunotherapy wherein the compound could be administered with together with the allergens to improve the development of tolerance, desensitization or immune deviation towards the allergen.

Further examples of allergens contemplated within the scope of the present invention are disclosed in WO 2006/085983 including ragweed allergen or grass allergen. Ragweed, and in particular Short Ragweed (*Ambrosia artemisiifolia*), is clinically the most important source of seasonal aeroallergens, as it is responsible for both the majority of cases and the most severe cases of allergic rhinitis (Pollart, et al. (1989) J. Allergy Clin. Immunol. 83(5):875-82; Rosenberg, et al. (1983) J. Allergy Clin. Immunol. 71(3):302-10; Bruce, et al. (1977) J. Allergy Clin. Immunol. 59(6): 449-59). Ragweed pollen also contributes significantly to exacerbation of asthma and allergic conjunctivitis.

Other exemplary food, animal, tree, insect and mold allergens are found at <http://www.allergen.org/List.htm> Marsh and Freidhoff. 1992. ALBE, an allergen database. (IUIS, Baltimore, Md., Edition 1.0).

The immunogen can further be an autoantigen (for example, to enhance self-tolerance to an autoantigen in a subject, e.g., a subject in whom self-tolerance is impaired). Examples of autoantigens contemplated within the scope of the present invention are disclosed in WO 2006/085983 including, without being limited to, actin, myelin basic protein, islet cell antigens, insulin, collagen and human collagen glycoprotein 39, muscle acetylcholine receptor and its separate polypeptide chains and peptide epitopes, glutamic acid decarboxylase and muscle-specific receptor tyrosine kinase, nicotinic acetylcholine receptor, transglutaminase, oxoglutarate dehydrogenase complex, branched-chain alpha-keto acid dehydrogenase complex, apolipoprotein H, nucleoprotein 62, RA33, Sp100 nuclear antigen and nucleoporin 210kDa.

The adjuvant according to the present invention represented by a compound of formula (I) as described herein in the various embodiments, can be used for a variety of purposes and administered in various way well known to those skilled in the art.

An exemplary disclosure of purposes and methods for administering an adjuvant is provided in WO 2006/085983. In particular, the adjuvant according to the invention may be used generally in active or passive immunization for producing antibodies *in vivo* or *in vitro*, or in methods of producing antibodies against an immunogen for any other purpose, e.g., for diagnostics or for use in histological techniques.

The adjuvant may further be used in human or veterinary therapy or prophylaxis. In particular, the adjuvant of the invention can be administered to a subject as a general immune enhancer to increase both innate and adaptive immune function in the subject, for example, in immunocompromised subjects such as subjects undergoing chemotherapy, radiation therapy, subjects with chronic infections (e.g., HCV and HBV) and/or subjects with HIV/AIDs. The invention can further be practiced to enhance the immune response to an attenuated live virus, a killed vaccine, or a DNA vaccine, all of which can have the disadvantage of reduced immunogenicity. The adjuvant of the invention can further be used to treat a chronic or latent infection to induce or enhance the immune response against the antigen(s) produced by the infection.

Brief Description of the Figures

Figure 1. shows the clearance of influenza virus from lung tissue of mice after treatment with propionate.

Figure 2. shows the number of CD4+ T cells in the lung of mice responding to Influenza infection after treatment with propionate.

Figure 3. shows the percentage of Influenza-specific CD8+ T cells within the total CD8+ T cell population of cells in the lung of treated mice during influenza infection.

Figure 4. shows the number of memory Influenza-specific CD8+ T cells in the lung of treated mice during secondary infections (vaccination strategy).

Figure 5 shows the results of propionate treatment of mice sensitized and challenged to Fel d 1. Data is an ELISA measurement of Fel d 1-specific IgE in serum samples on day 4 post intranasal administration of Fel d 1 in Fel d 1 presensitized mice. Propionate treatment significantly reduces circulating levels of allergen (Fel d 1)-specific IgE in treated mice.

Figure 6 shows the results of propionate treatment of mice sensitized and challenged to Fel d 1. Data is an ELISA measurement of Fel d 1-specific IgA in BAL fluid samples on day 4 post intranasal administration of Fel d 1 in Feld-1 presensitized mice. Propionate treatment significantly increases levels of allergen (Fel d 1)-specific IgA in the airways of treated mice.

Figure 7 shows the results of propionate treatment of mice sensitized and challenged to Fel. Data is an ELISA measurement of Fel d 1-specific IgG2c in serum samples on day 4 post

intranasal administration of Fel d 1 in Feld-1 presensitized mice. Treatment with propionate does not effect levels of allergen (Fel d 1)-specific IgG2a/c in the serum

Figure 8 shows the results of propionate treatment of Feld-1 presensitized mice. Data is from a Bioplex assay of BAL fluid on day 4 post intranasal administration of Fel d 1 in Feld-1 presensitized mice. Propionate treatment reduces the amount of the prototypic Th2 cytokine, IL-4, in the airways.

Figure 9 shows the results of propionate treatment of Feld-1 presensitized mice. Data is from a Bioplex assay of BAL fluid on day 4 post intranasal administration of Fel d 1 in Feld-1 presensitized mice. Propionate treatment reduces the amount of the cytokine, IL-17A, in the airways.

Figure 10 shows the results of propionate treatment of Feld-1 presensitized mice. Data is from a Bioplex assay of BAL fluid on day 4 post intranasal administration of Fel d 1 in Feld-1 presensitized mice. Propionate treatment reduces the amount of the chemokine, CXCL1 (the mouse orthologue of IL-8), in the airways.

Figure 11 shows the results of propionate treatment of Feld-1 presensitized mice. Data is from total and differential cell counts of cells in the BAL fluid on day 4 post intranasal administration of Fel d 1 in Feld-1 presensitized mice. Addition of propionate to drinking water of mice for 2 weeks prior to the induction of asthma reduces the number of eosinophils that infiltrate into the airways following allergen challenge.

Figure 12 shows the results of propionate treatment of Feld-1 presensitized mice. Data is from total and differential cell counts of cells in the BAL fluid on day 4 post intranasal administration of Fel d 1 in Feld-1 presensitized mice. Injection of propionate 3 times per week for 2 weeks prior to the induction of asthma reduces the number of eosinophils that infiltrate into the airways following allergen challenge.

Figure 13 shows the results of propionate treatment of Feld-1 presensitized mice. Data is from total and differential cell counts of cells in the BAL fluid on day 4 post intranasal administration of Fel d 1 in Feld-1 presensitized mice. Injection of either sodium propionate or the derivative 2,2-D2 propionic acid 3 times per week for 2 weeks prior to the induction of asthma reduces the number of eosinophils that infiltrate into the airways following allergen challenge.

Figure 14 shows the results of propionate treatment of Feld-1 presensitized mice. Sodium propionate treatment protects against the sustained recruitment of inflammatory cells into the airways following exposure to allergens.

Figure 15 shows the results of propionate treatment of Feld-1 presensitized mice. Sodium propionate treatment protects against the sustained recruitment of eosinophils into the airways following exposure to allergens.

Figure 16 shows the results of propionate treatment of Feld-1 presensitized mice. Treatment with sodium propionate reduces the production of IL-5, IL-13, IL-4 and IL-17 following restimulation of lymph node cells isolated from a house-dust mite allergic mouse.

Figure 17 shows the results of propionate treatment of Feld-1 presensitized mice. Treatment with sodium propionate alters the number of CD11c+ dendritic cells in the airways of mice following allergen exposure.

Figure 18 shows the results of propionate treatment of Feld-1 presensitized mice. Treatment with sodium propionate reduces MHC class II expression on dendritic cells in the airways of mice following allergen exposure.

Figure 19 shows the results of propionate treatment of Feld-1 presensitized mice. Dendritic cells isolated from the lungs of mice previously treatment with sodium propionate are less effective at reactivating CD4+ T cells.

EXAMPLES:Materials and Methods

The compounds of formula (I) can be manufactured by methods known in the art. Starting materials are either commercially available or can be prepared by methods known in the art.

Propionate: Sodium propionate can be obtained commercially or manufactured by methods known in the art.

Measurement of antibodies:*Fel d 1-ELISA.*

1. Coat flat bottom 96-well plate (NUNC-Immuno MaxiSorp) with 5µg/ml Fel d 1 final in 100µl/well using Carbonate buffer pH 9.6 (see recipe below).
2. Incubate O/N at 4°C.
3. Wash 4X with PBS/0.05% tween.
4. Block plate for 2H at RT with 200µl/well of PBS/0.05% Tween/1% BSA.
5. Make serial dilutions of your samples in PBS (usually 1 :10, 1 :100, 1 :1'000 and 1 :10'000 for sera and 1 :10 and 1 :100 for BALF).
6. Wash 4X with PBS/0.05% Tween.
7. Add 100µl/well of diluted samples (in duplicates).

Note : Keep some wells to do test have a background control = blank (only PBS).

8. Incubate 2H at RT.
9. Wash 4X with PBS/0.05% Tween.
10. Add 100µl/well of Alkaline Phosphatase (AP)-conjugated anti-mouse IgG1, IgG2c, IgA or biotinylated anti-mouse IgE, all diluted at 1 :1'000 in PBS/0.2% BSA.
11. Incubate for 2H at RT.
12. Wash 4X with PBS/0.05% Tween the wells with Biotinylated anti-mouse IgE only and add 100µl/well of AP-conjugated streptavidin diluted at 1 :1'000 in PBS/0.2% BSA.
13. Incubate 20min at RT.
14. Wash 4X with PBS/0.05% Tween.
15. Dissolve 1 Alkaline Phosphatase Substrate Tablet (Sigma, cat. # N2765-100TAB) into 20ml of TM Buffer.
16. Add 100µl per well.
17. Develop in the dark and read at 405nm.

Carbonate Buffer recipe: 8.4g NaHCO₃, 3.56g Na₂CO₃ qsp 1 Liter with ddH₂O. pH to 9.6 and store at 4°C.

TM Buffer recipe: 121.1g Tris Base, 1ml 0.3M MgCl₂ qsp 1 Liter ddH₂O. pH to 9.8.

Cytokine and chemokine measurement: BAL fluid was measured for specific cytokines utilizing a LegendPlex assay (Biolegend) following manufacturers instructions.

Collection and analysis of bronchoalveolar lavage (BAL) cells.

BAL was performed by flushing the airways three times with 1 ml PBS. Total BAL cells were counted using a Coulter Counter (IG Instruments) and spun onto glass slides using a Cytospin 2 (Shandon Southern Products, Ltd.). Cells were then stained with Diff Quick staining set (Siemens-Dade Behring). Percentages of eosinophils, macrophages, lymphocytes and neutrophils were determined microscopically using standard morphological and cytochemical criteria.

PART I Treatment of Viral InfectionsExample 1: Infection of mice and administration of propionate

C57BL/6 mice (supplied by Charles Rivers laboratories) were treated with sodium propionate (1g/kg) or saline via intraperitoneal injection 3 times per week. Following two weeks of treatment, mice were anesthetized with ketamine/xylazine and infected with 100 pfu Influenza virus strain PR8 (A/Puerto Rico8/34, H1N1) via intranasal inoculation.

Example 2: Determination of viral load in the lung

Mice were sacrificed on day 10 post infection with a lethal injection of pentobarbital and the viral load in the lung tissue was determined by quantitative PCR. RNA was prepared with TRI-Reagent (Molecular Research Center Inc.) and then treated with DNase (Invitrogen, USA) to avoid genomic DNA contamination before RNA was converted to cDNA by reverse transcription using SuperScript III (Invitrogen, USA). cDNA was quantified by real-time PCR (I-cycler, Biorad, USA) using SYBR Green (Stratagene, USA) and samples were normalized with GAPDH expression levels. Primers sequences used: GAPDH 5'-GGGTGTGAACACGAGAAAT-3' and 5'-CCTTCCACAATGCCAAAGTT-3'; Influenza PR8 M protein 5'-GGAAGTGCAGCGTAGACGCTT-3' and 5'-CATCCTGTATATGAGGCCCAT-3' as previously described van Elden, L. J., M. Nijhuis, P. Schipper, R. Schuurman, A. M. van Loon. 2001. Simultaneous detection of influenza viruses A and B using real-time quantitative PCR. *J. Clin. Microbiol.* 39: 196-200.

Example 3: Determination of CD4+ T cell number

C57BL/6 mice were treated as described in Example 1. The number of CD4+ T cells infiltrating into the airways at day 10 post infection was determined by FACS analysis. Specifically, a small incision on the trachea was performed through which a catheter was introduced. The lungs were flushed with 1mL PBS. BAL cells were harvested by centrifugation. Total cell numbers per BAL were determined by Coulter Counter (IG Instrumenten Gesellschaft AG), and cells were processed for further analysis. CD4-FITC

(eBioscience) was subsequently added for 20min at 4°C. Cells were washed and analysed by flow cytometry (FACSCalibur; Becton Dickinson).

Example 4: Determination of Determination of CD8+ T cell number during primary infection

C57BL/6 mice were treated as described in Example 1. The number of Influenza-specific tetramer+ CD8+ T cells infiltrating into the lungs at day 10 post infection was determined by FACS analysis. Specifically, BAL cells were incubated with 10µg/mL NP34+ PE-conjugated Tetramers for 40min at 4°C. CD8-APC (eBioscience) was subsequently added for 20min at 4°C. Cells were washed and analysed by flow cytometry (FACSCalibur; Becton Dickinson).

Example 5: Determination of Determination of CD8+ T cell number during secondary infection

C57BL/6 mice were given propionate, 200mM in drinking water, for two weeks prior to infection and throughout the whole study. Mice were infected with 100 pfu Influenza virus strain PR8 via intranasal inoculation. Four weeks following infection, mice were infected with the serotypically distinct Influenza virus strain X31 (A/68, H3N2). The number of memory influenza-specific tetramer+ CD8+ T cells infiltrating into the lungs at day 3 post infection was determined by FACS analysis as described in Example 4.

Example 6: Results 1

6.1 Propionate treatment was shown to accelerate the clearance of influenza virus from lung tissue of mice artificially treated with 100 pfu Influenza virus strain PR8 (A/Puerto Rico8/34, H1N1) via intranasal inoculation (Figure 1).

6.2 Propionate treatment was further shown to increases the number of CD4+ T cells in the lung of artificially infected mice responding to Influenza infection (Figure 2).

6.3 Propionate treatment was further shown to increases the percentage of Influenza-specific CD8+ T cells within the total CD8+ T cell population of cells in the lung of artificially infected mice during influenza infection (Figure 3.)

6.4 Propionate treatment was also shown to increases the number of memory Influenza-specific CD8+ T cells in the lung of artificially infected mice during secondary infections (vaccination strategy) (Figure 4).

PART II Treatment of Allergic Disorders

Example 7: Administration of Propionate

Short-chain fatty acids such as propionic acid are end products of colonic anaerobic bacterial fermentation of dietary fibers (unabsorbed starch and non-starch polysaccharides). Bacteria of the *Bacteroidetes* phylum produce high levels of propionic acid.

In order to determine whether propionic acid has a modulatory activity on inflammatory pathways associated with allergy, sodium propionate was administered to model mice. Propionate can be administered orally or via injection.

7.1: In a first set of experiments, C57BL/6 mice were given either 200mM sodium propionate in drinking water, or 1g/kg sodium propionate intraperitoneally for 2 weeks prior to immunization and throughout the experiment.

7.2: In a second set of experiments, mice were given 150mM acetate, butyrate or propionate in drinking water for 2 weeks or 1g/kg propionate intraperitoneally every other day for 2 weeks prior to immunization and throughout the experiment.

Example 8: Immunization Protocol

8.1/8.2: Experimental mice were immunized intraperitoneally with 1µg Fel d 1 or OVA antigen in alum adjuvant. Seven days later, mice were challenged with 10µg Fel d 1 in saline. Four days after challenge, mice were sacrificed. Bronchoalveolar lavage fluid was collected to determine BAL total and differential cell counts. Systemic and lung lavage fluid Fel d 1-specific IgE, IgG2c, and IgA levels were quantified by ELISA.

Control mice received either saline vehicle in drinking water or by injection.

Example 9: Results

Propionate was shown to be capable of reducing a range of different inflammatory pathways associated with allergy.

9.1. Propionate does not function as a general immunosuppressive molecule, and shows selective control of allergen-specific IgE (Figure 5) and IgA (Figure 6) antibody production, whilst leaving other important antibody isotypes such as IgG2a and IgG2c unaffected (Figure 7), thus not compromising immunity against pathogens such as viruses.

9.2. Propionate treatment was shown to reduce the release of Th2 cytokines such as IL-4 and IL-17A in the airways (Figure 8 and 9). Propionate treatment was further shown to

reduce the release of the neutrophil recruiting chemokine KC (mouse orthologue of IL-8) in the airways (Figure 10).

9.3. Propionate treatment was also shown to reduce the number of eosinophils that infiltrate into the airways following allergen challenge. (Figures 11-13)

Example 10:

Mice were treated with sodium propionate at 1g/kg for two weeks every other day. Mice were exposed to house-dust mite extract (HDM) three times per week over two weeks. On the indicated days following the last exposure to HDM BAL was performed and the total number of cells in the airways were counted. Animals treated with sodium propionate exhibit a reduced duration of the inflammatory infiltrate (Figure 14). These data highlight the use of sodium propionate in the treatment of chronic inflammation.

Example 11

Mice were treated with sodium propionate at 1g/kg for two weeks every other day. Mice were exposed to house-dust mite extract (HDM) three times per week over two weeks. On the indicated days following the last exposure to HDM BAL was performed and the proportion of different cell types was determined using standard morphological techniques. Animals treated with sodium propionate exhibit a reduction in the magnitude and duration of airway eosinophil infiltration (Figure 15).

Example 12

Mice were treated with sodium propionate at 1g/kg for two weeks every other day. Mice were exposed to house-dust mite extract (HDM) three times per week over two weeks. On the indicated days following the last exposure to HDM BAL was performed and the total number of cells in the airways were counted.

Example 13

Mice were treated with sodium propionate at 1g/kg for two weeks every other day. Mice were exposed to house-dust mite extract (HDM) three times per week over two weeks. Four days following the last exposure to HDM the draining mediastinal lymph nodes were removed, cells were isolated and restimulated for 3 days in the presence of HDM. The indicated cytokine levels in the supernatant were measured by Luminex bioplex. Animals treated with sodium propionate reduces the capacity of cells to produce the cytokines IL-5, IL-13, IL-4 and IL-17A (Figure 16).

Example 14

Mice were treated with sodium propionate at 1g/kg for two weeks every other day. Mice were exposed to house-dust mite extract (HDM) three times per week over two weeks. Following exposure, lungs were removed and dendritic cells were identified by their expression of CD11b and CD11c by flow cytometry. Total numbers of dendritic cells were determined. Treatment with sodium propionate reduces the number of proinflammatory dendritic cells in the airways (Figure 17).

Example 15

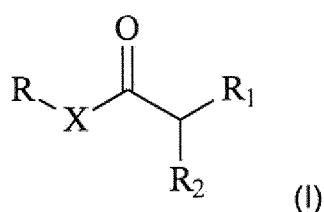
Mice were treated with sodium propionate at 1g/kg for two weeks every other day. Mice were exposed to house-dust mite extract (HDM) three times per week over two weeks. Following exposure, lungs were removed and dendritic cells were identified by their expression of CD11b and CD11c and the level of MHCII on the cell surface was determined by flow cytometry. Treatment with sodium propionate reduces the expression of MHC class II on proinflammatory dendritic cells in the airways (Figure 18).

Example 16

Mice were treated with sodium propionate at 1g/kg for two weeks every other day. Mice were exposed to house-dust mite extract (HDM) three times per week over two weeks. In the last exposure, HDM was given in combination with OVA protein. One day following exposure, lungs were removed and dendritic cells were purified by flow cytometric sorting. Purified lung dendritic cells were cultured with previously activated OVA-specific T cells for 3 days and T cell proliferation was determined by ³H Thymidine uptake over the final 16 hours of culture. Treatment with sodium propionate reduces the ability of airway dendritic cells to induce the proliferation of effector CD4⁺ T cells (Figure 19).

CLAIMS

1. A compound of formula (I)



wherein

X represents -O-, -S-, or -NH-, preferably -O-;

R represents hydrogen, alkyl, aryl, arylalkyl, polyalkylene glycol;

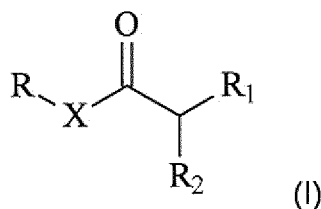
R₁ represents hydrogen, alkyl, hydroxyalkyl, arylalkyl, carboxylic acid;

R₂ represents hydrogen, alkyl, -O-R₃; and

R₃ represents hydrogen, aryl, arylalkyl, hydroxyalkyl-carboxyl;

or pharmaceutically acceptable salts thereof, for modulation of a Th2 or Th2-like immune response towards a Th1 immune response.

2. The compound of formula (I) according to claim 1



wherein

X represents -O-, -S-, or -NH-, preferably -O-;

R represents hydrogen, alkyl, aryl, arylalkyl, polyalkylene glycol;

R₁ represents hydrogen, alkyl, hydroxyalkyl, arylalkyl, carboxylic acid;

R₂ represents hydrogen, alkyl, -O-R₃; and

R₃ represents hydrogen, aryl, arylalkyl, hydroxyalkyl-carboxyl;
or pharmaceutically acceptable salts thereof, use in the prevention, attenuation or treatment of a viral infection and/or virus-induced exacerbations of allergic diseases or disorders such as asthma, chronic obstructive pulmonary disease and autoimmunity.

3. The compound of claim 1 or 2, wherein
X represents -O-, -S-, or -NH-, preferably -O-;
R represents hydrogen, alkyl, aryl, arylalkyl, polyalkylene glycol;
R₁ represents hydrogen, alkyl, hydroxyalkyl;
R₂ represents hydrogen, alkyl, -O-R₃; and
R₃ represents hydrogen, aryl, arylalkyl, hydroxyalkyl-carboxyl;
or pharmaceutically acceptable salts thereof.
4. The compound of claim 3, wherein
X represents -O-, -S-, or -NH-, preferably -O-;
R represents hydrogen, C₁-C₆ alkyl, unsubstituted or substituted phenyl with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano, C₁-C₄ alkyloxy or trifluoro;
R₁ represents hydrogen, C₁-C₆ alkyl, hydroxy-C₁-C₆ alkyl wherein the alkyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of hydroxyl, amino, carboxylic acid, halogen, cyano, or nitro;
R₂ represents hydrogen, C₁-C₆ alkyl, -O-R₃; and
R₃ represents hydrogen, unsubstituted or substituted phenyl with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano, C₁-C₄ alkyloxy or trifluoro, phenyl-C₁-C₆ alkyl wherein the phenyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano, C₁-C₄ alkyloxy or trifluoro, hydroxy-C₁-C₆ alkyl-carboxyl;
or pharmaceutically acceptable salts thereof.
5. The compound of claim 4, wherein
X is -O-,
R is hydrogen;
R₁ represents hydrogen, C₁-C₄ alkyl, hydroxy-C₁-C₄ alkyl wherein the alkyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of hydroxyl, amino, or carboxylic acid, preferably hydroxyl and/or carboxylic acid; and
R₂ is hydrogen or C₁-C₄ alkyl;

or pharmaceutically acceptable salts thereof.

6. The compound of claim 4, wherein

X is -O-,

R is hydrogen;

R₁ represents hydrogen, C₁-C₄ alkyl, hydroxy-C₁-C₄ alkyl wherein the alkyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of hydroxyl, amino or carboxylic acid, preferably hydroxyl and/or carboxylic acid; and

R₂ is -OR₃; and

R₃ represents hydrogen, unsubstituted or substituted phenyl with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano or methoxy, phenyl-C₁-C₄ alkyl wherein the phenyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano or methoxy, hydroxy-C₁-C₃ alkyl-carboxyl;

or pharmaceutically acceptable salts thereof.

7. The compound of claim 4, wherein

X is -O-,

R is hydrogen;

R₁ represents hydrogen, C₁-C₃ alkyl, hydroxy-C₁-C₃ alkyl wherein the alkyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of hydroxyl and/or carboxylic acid; and

R₂ is hydrogen or C₁-C₄ alkyl;

or pharmaceutically acceptable salts thereof.

8. The compound of claim 4, wherein

X is -O-,

R is hydrogen;

R₁ represents hydrogen, C₁-C₃ alkyl, hydroxy-C₁-C₃ alkyl wherein the alkyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of hydroxyl or carboxylic acid;

R₂ is -OR₃; and

R₃ represents hydrogen, unsubstituted or substituted phenyl with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano or methoxy, phenyl-C₁-C₄ alkyl wherein the phenyl group may be unsubstituted or substituted with one or more, same or different, substituents selected

from the group consisting of nitro, halogen, amino, hydroxyl, cyano, or methoxy, hydroxy-C₁-C₃ alkyl-carboxyl;
or pharmaceutically acceptable salts thereof.

9. The compound of claim 4, wherein

X is -O-,

R is hydrogen;

R₁ is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, isopropyl, hydroxymethyl, dihydroxymethyl, hydroxyethylcarboxylic acid, methylcarboxylic acid, hydroxymethylcarboxylic, ethylcarboxylic acid; and

R₂ is selected from the group consisting of hydrogen, hydroxyl or methyl;
or pharmaceutically acceptable salts thereof.

10. The compound of claim 4, wherein

X is -O-,

R is hydrogen;

R₁ is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, isopropyl;

R₂ is -OR₃; and

R₃ is selected from the group consisting of 1-hydroxyethylcarbonyl, benzyl, nitrophenyl;
or pharmaceutically acceptable salts thereof.

11. The compound of claim 4, wherein

X is -O-,

R represents C₁-C₄ alkyl, unsubstituted or substituted phenyl with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano or methoxy, phenyl-C₁-C₄ alkyl wherein the phenyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of halogen, nitro, amino, hydroxyl, cyano or methoxy, polyalkylene glycol;

R₁ is C₁-C₄ alkyl or hydroxy-C₁-C₄ alkyl, wherein the alkyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of hydroxyl, amino or carboxylic acid; and

R₂ is hydrogen;

or pharmaceutically acceptable salts thereof

12. The compound of claim 4, wherein

X is -O-,

R represents C₁-C₄ alkyl, unsubstituted or substituted phenyl with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino,

hydroxyl, cyano or methoxy, phenyl-C₁-C₄ alkyl wherein the phenyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of halogen, nitro, amino, hydroxyl, cyano or methoxy, polyalkylene glycol;

R₁ is C₁-C₃ alkyl or hydroxy-C₁-C₃ alkyl wherein the alkyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of hydroxyl and/or carboxylic acid; and

R₂ is hydrogen;

or pharmaceutically acceptable salts thereof.

13. The compound of claim 4, wherein

X is -O-,

R is selected from the group consisting of methyl, ethyl, propyl, benzyl, nitrobenzyl, polyethylene glycol;

R₁ selected from the group consisting of ethyl, hydroxyethyl; and

R₂ is hydrogen;

or pharmaceutically acceptable salts thereof

14. The compound of claim 4 selected from the group consisting of

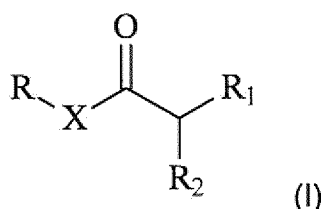
acetic acid, propionic acid, butyric acid, isobutyric acid, 2-hydroxypropionic acid, dilactic acid, 2-benzyloxypropionic acid, 2-(*p*-nitrophenyl)-oxy-propionic acid, 3-hydroxypropionic acid, 2,3-dihydroxypropionic acid, methyl 3-hydroxypropionate, ethyl 3-hydroxypropionate, propyl 3-hydroxypropionate, benzyl 3-hydroxypropionate, para-nitrophenyl 3-hydroxypropionate, *p*-nitrobenzyl 3-hydroxypropionate, polyethylene glycol 3-hydroxypropionate, methyl propionate, ethyl propionate, propyl propionate, benzyl propionate, *p*-nitrophenyl propionate, *p*-nitrobenzyl propionate, 2-(4-Isobutylphenyl) propionic acid, lactic acid, citric acid, malic acid, malonic acid, succinic acid, and tartaric acid; or pharmaceutical acceptable salts thereof.

15. The compound of claim 14, which is propionic acid, isobutyric acid, 3-hydroxypropionic acid, 2,3-dihydroxypropionic acid, lactic acid, or citric acid.
16. The compound of any one of claims 1-15 for use in the prevention, attenuation or treatment of a viral infection.
17. The compound of any one of claims 1-15 for use in the prevention, attenuation or treatment virus-induced exacerbations of allergic diseases or disorders such as asthma, chronic obstructive pulmonary disease and autoimmunity.
18. The compound of claim 16 or claim 17, wherein said viral infection or virus-induced exacerbations of allergic diseases or disorders is caused by a virus selected from the

group consisting of Influenza virus, respiratory syncytial virus, human immunodeficiency virus, vaccina virus, variola virus, dengue virus, coxsackie virus, hepatitis A virus, poliovirus, rhinovirus, Herpes simplex, type 1, Herpes simplex, type 2, Varicella-zoster virus, Epstein-barr virus, Human cytomegalovirus, Human herpesvirus, Hepatitis B virus, Hepatitis C virus, yellow fever virus, dengue virus, West Nile virus, Measles virus, Mumps virus, Parainfluenza virus, Human metapneumovirus, Human papillomavirus, Rabies virus, Rubella virus, Human bocavirus, and Parvovirus B19.

19. A composition comprising a compound of any one of claims 1-15 in a pharmaceutically effective amount optionally together with a pharmaceutically acceptable carrier for modulation of a Th2 or Th2-like immune response towards a Th1 immune response.
20. A composition comprising a compound of any one of claims 1-15 optionally together with a pharmaceutically acceptable carrier for treatment, prevention, or attenuation of viral infections and/or virus-induced exacerbations of allergic diseases or disorders such as asthma, chronic obstructive pulmonary disease and autoimmunity.
21. A method of using a compound of any one of claims 1-15 or a composition of any of claims 19-20 in the preparation of a medicament for modulation of a Th2 or Th2-like immune response towards a Th1 immune response.
22. The method of claim 21 for inducing antigen-specific T cells, particularly of antigen-specific CD4+ T cells or CD8+ T cells or both, in a subject in need thereof comprising administering to a subject a compound of any one of claims 1-15 or a composition of claim 19 or claim 20.
23. The method of claim 21 for preventing, attenuating or treating of viral infections and/or virus-induced exacerbations of allergic diseases or disorders such as asthma, chronic obstructive pulmonary disease and autoimmunity comprising administering to a subject in need thereof a compound of any one of claims 1-15 or a composition of claim 19 or claim 20.
24. The method of claim 23, wherein said viral infection or virus-induced exacerbations of allergic diseases or disorders is caused by a virus selected from the group consisting of Influenza virus, respiratory syncytial virus, human immunodeficiency virus, vaccina virus, variola virus, dengue virus, coxsackie virus, hepatitis A virus, poliovirus, rhinovirus, Herpes simplex, type 1, Herpes simplex, type 2, Varicella-zoster virus, Epstein-barr virus, Human cytomegalovirus, Human herpesvirus, Hepatitis B virus, Hepatitis C virus, yellow fever virus, dengue virus, West Nile virus, Measles virus, Mumps virus, Parainfluenza virus, Human metapneumovirus, Human papillomavirus, Rabies virus, Rubella virus, Human bocavirus, and Parvovirus B19.

25. A compound according to any one of claims 1-15 for use as an adjuvant in inducing, promoting or enhancing an immune response to an immunogen in a subject, for example, an immunogen comprised in a vaccine, particularly a viral vaccine.
26. A composition comprising the compound of claim 25 optionally together with a pharmaceutically acceptable carrier for use as an adjuvant in inducing, promoting or enhancing an immune response to an immunogen in a subject, for example, an immunogen comprised in a vaccine, particularly a viral vaccine.
27. The composition of claim 20 or claim 26, which is an oral nutritional composition.
28. The composition of claim 27, wherein the composition is a beverage, a drink, a bar, a snack, an ice cream, a dairy product, for example a chilled or a shelf-stable dairy product, a fermented dairy product, a drink, for example a milk-based drink, an infant formula, a growing-up milk, a confectionery product, a chocolate, a cereal product such as a breakfast cereal, a sauce, a soup, an instant drink, a frozen product intended for consumption after heating in a micro-wave or an oven, a ready-to-eat product, a fast food or a nutritional formula.
29. A method of inducing, promoting or enhancing an immune response to an immunogen in a subject, for example, an immunogen comprised in a vaccine, particularly a viral vaccine comprising administering to a subject in need thereof a compound of claim 25, or a composition of claim 26.
30. The method of any one of claims 21-24 and of claim 29, wherein the administration of said compound or composition is effected by oral, parenteral, subcutaneous, intraperitoneal, topical, transmucosal, transdermal, intrabronchial, intrapulmonary and intranasal, intraventricular, intraarticular, intrathecal, intravaginal, intratracheal, administration and, if desired for local treatment, intralesional administration
31. The method of claim 30, wherein the administration of said compound or composition is effected by oral administration, particularly in form of an oral nutritional composition.
32. The method of claim 31, wherein said compound or composition is administered admixed to food, functional food, drinks or medicinal food.
33. A compound of formula (I)



wherein

X represents -O-, -S-, or -NH-, preferably -O-;

R represents hydrogen, alkyl, aryl, arylalkyl, polyalkylene glycol;

R₁ represents hydrogen, alkyl, hydroxyalkyl, arylalkyl, carboxylic acid;

R₂ represents hydrogen, alkyl, -O-R₃; and

R₃ represents hydrogen, aryl, arylalkyl, hydroxyalkyl-carboxyl;

or a pharmaceutically acceptable salt thereof for use in a method for the prevention of development of a Th2 induced inflammatory condition in a tissue or organ of a subject, the method comprising administering an effective amount of a compound of formula (I) to the subject, which compound modulates the number and/or the activation state of dendritic cells (DCs) in the affected tissue or organ, particularly prior to the activation of a T cell response.

34. The compound of claim 33, wherein

X represents -O-, -S-, or -NH-, preferably -O-;

R represents hydrogen, C₁-C₆ alkyl, unsubstituted or substituted phenyl with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano, C₁-C₄ alkyloxy or trifluoro;

R₁ represents hydrogen, carboxylic acid, C₁-C₆ alkyl, hydroxy-C₁-C₆ alkyl wherein the alkyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of hydroxyl, amino, carboxylic acid, halogen, cyano, or nitro;

R₂ represents hydrogen, C₁-C₆ alkyl, -O-R₃; and

R₃ represents hydrogen, unsubstituted or substituted phenyl with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano, C₁-C₄ alkyloxy or trifluoro, phenyl-C₁-C₆ alkyl wherein the phenyl group may be unsubstituted or substituted with one or more, same or different, substituents selected from the group consisting of nitro, halogen, amino, hydroxyl, cyano, C₁-C₄ alkyloxy or trifluoro, hydroxy-C₁-C₆ alkyl-carboxyl;

or pharmaceutically acceptable salts thereof.

35. The compound of claim 34, wherein

X is -O-,

R is hydrogen;

R₁ is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, isopropyl, hydroxymethyl, dihydroxymethyl, hydroxyethyl, dicarboxylic acid, carboxylic acid, methylcarboxylic acid, hydroxymethylcarboxylic, ethylcarboxylic acid; and

R₂ is selected from the group consisting of hydrogen, hydroxyl or methyl;
or pharmaceutically acceptable salts thereof.

36. The compound of claim 34, wherein

X is -O-,

R is selected from the group consisting of methyl, ethyl, propyl, benzyl, nitrobenzyl, polyethylene glycol;

R₁ selected from the group consisting of methyl, hydroxymethyl; and

R₂ is hydrogen;

or pharmaceutically acceptable salts thereof

37. The compound of claim 34, wherein

X is -O-,

R is hydrogen;

R₁ is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, isopropyl;

R₂ is -OR₃; and

R₃ is selected from the group consisting of 1-hydroxyethylcarbonyl, benzyl, nitrophenyl;
or pharmaceutically acceptable salts thereof.

38. The compound of claim 34 selected from the group consisting of acetic acid, propionic acid, butyric acid, isobutyric acid, 2-hydroxypropionic acid, dilactic acid, 2-benzyloxypropionic acid, 2-(*p*-nitrophenyl)-oxy-propionic acid, 3-hydroxypropionic acid, 2,3-dihydroxypropionic acid, methyl 3-hydroxypropionate, ethyl 3-hydroxypropionate, propyl 3-hydroxypropionate, benzyl 3-hydroxypropionate, para-nitrophenyl 3-hydroxypropionate, *p*-nitrobenzyl 3-hydroxypropionate, polyethylene glycol 3-hydroxypropionate, methyl propionate, ethyl propionate, propyl propionate, benzyl propionate, *p*-nitrophenyl propionate, *p*-nitrobenzyl propionate, 2-(4-Isobutylphenyl) propionic acid, lactic acid, citric acid, malic acid, malonic acid, succinic acid, and tartaric acid; or pharmaceutical acceptable salts thereof.

39. The compound of claim 38, which is propionic acid, isobutyric acid, 3-hydroxypropionic acid, 2,3-dihydroxypropionic acid, lactic acid, or citric acid.

40. The compound of any one of claims 31-37, with the proviso that

R₁ and R₂ are not hydrogen when X is -O- and R is hydrogen; or

R₁ is not alkyl, R₂ is not hydrogen when X is -O- and R is hydrogen; or

R₁ and R₂ are not Me when X is NH and R is Ar; or

R₁ is not alkyl and R₂ is not hydrogen when X is NH and R is alkyl.

41. A composition comprising the compound of any one of claims 33-40 in a therapeutically effective amount together with a pharmaceutically acceptable salt thereof and, optionally, a pharmaceutically acceptable carrier for use in the treatment or prevention of a disease or disorder, particularly of an allergic disease or disorder, or for ameliorating the condition of a subject suffering from such a disease or disorder.
42. The composition of claim 41, which is an oral nutritional composition.
43. The composition of claim 42, wherein the composition is a beverage, a drink, a bar, a snack, an ice cream, a dairy product, for example a chilled or a shelf-stable dairy product, a fermented dairy product, a drink, for example a milk-based drink, an infant formula, a growing-up milk, a confectionery product, a chocolate, a cereal product such as a breakfast cereal, a sauce, a soup, an instant drink, a frozen product intended for consumption after heating in a micro-wave or an oven, a ready-to-eat product, a fast food or a nutritional formula.
44. The compound of any one of claims 33-40 or the composition of any one of claims 41-43 for reducing the amount of T helper 2 (Th2) cell-derived cytokines of a subject treated with said compound, particularly in the airways of said subject and thus for use in the prevention of a disease or disorder mediated by T helper 2 (Th2) cell-derived cytokines, or for amelioration of the condition of a subject suffering from such a disease or disorder.
45. The compound of any one of claims 33-40 or the composition of any one of claims 41-43 for reducing the circulating levels of immunogen-specific IgE in a subject treated with said compound and exposed to an immunogen, and thus for use in the prevention of an IgE mediated disease or disorder, or for amelioration of the condition of a subject suffering from such a disease or disorder.
46. The compound of any one of the claims 33-40 or the composition of any one of claims 41-43 for reducing the number of eosinophils in a subject treated with said compound and exposed to an immunogen, particularly in the airways of said subject, and thus for use in the prevention of an eosinophilic disease or disorder, or for amelioration of the condition of a subject suffering from such a disease or disorder.
47. The compound of any one of the claims 33-40, or the composition of any one of claims 41-43, wherein said disease or disorder is an allergic disease or disorder.
48. The compound according to any one of the claims 33-40 or the composition of any one of claims 41-43, wherein said disease or disorder is

- (a) an allergic disorders including autoimmune diseases selected from asthma, rhinitis, dermatitis, drug reactions, esophageal and gastrointestinal allergy;
 - (b) an allergic disease or disorder is a disease or disorder selected from the group consisting of allergic asthma, hay fever, drug allergies, allergic bronchopulmonary aspergillosis (ABPA), esophageal and a gastrointestinal allergy, pemphigus vulgaris, atopic dermatitis, onchocercal dermatitis, or a combination thereof;
 - (c) an IgE-mediated disease or disorder selected from the group consisting of urticaria, eczema conjunctivitis, rhinorrhea, rhinitis, particularly allergic rhinitis, gastroenteritis, or a combination thereof;
 - (d) an IgE-mediated disease or disorder selected from the group consisting of myeloma, multiple myeloma, Hodgkin's disease, Hyper-IgE syndrome, Wiskott-Aldrich syndrome, or a combination thereof; and
 - (e) an eosinophilic disease or disorder selected from the group consisting of nodules, eosinophilia, eosinophilic rheumatism, dermatitis and swelling (NERDS).
49. A method for the prevention of development of a Th2 induced inflammatory condition in a tissue or organ of a subject, the method comprising administering an effective amount of a compound of formula (I) as defined in any one of claims 33-40 or a composition of any one of claims 41-43 to the subject, which compound modulates the number and/or the activation state of dendritic cells (DCs) in the affected tissue or organ, particularly prior to the activation of a T cell response.
50. The method of claim 49, wherein the release of cytokines from Th2 cells and/or systemic IgE levels is reduced, while other antibody isotypes, including IgG2a, IgG2c and IgA, are left unaffected, and/or eosinophil infiltration into the tissues or organs is reduced.
51. The method of claim 49 or claim 50, resulting in the treatment or prevention of an associated disease or disorder or amelioration of the condition of a subject suffering from such a disease or disorder, particularly an allergic disease or disorder.
52. The method of claim 49, for use in the treatment or prevention of a disease or disorder mediated by IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, and/or IL-17A, particularly IL-4 and/or IL-8 and/or IL-17A, or for ameliorating the condition of a patient suffering from such a disease or disorder.
53. The method of claim 49, for use in selective control of allergen-specific IgE antibody levels in a subject suffering from IgE-mediated disease or disorder.

54. The method of claim 49, wherein the IgG and/or IgA levels in the treated subject remain unaffected or are increased.
55. The method of claim 52, for use in reducing the IL-4 release from Th2 cells in a subject suffering from an IL-4 mediated disease or disorder.
56. The method of claim 49, for use in the treatment or prevention of an eosinophilic disease or disorder, or for ameliorating the condition of a patient suffering from such a disease or disorder.
57. The method according to any one of the claims 49-56, wherein said disease or disorder is
- (a) an allergic disorders including autoimmune diseases selected from asthma, rhinitis, dermatitis, drug reactions, esophageal and gastrointestinal allergy;
 - (b) an allergic disease or disorder is a disease or disorder selected from the group consisting of allergic asthma, hay fever, drug allergies, allergic bronchopulmonary aspergillosis (ABPA), esophageal and a gastrointestinal allergy, pemphigus vulgaris, atopic dermatitis, onchocercal dermatitis, or a combination thereof;
 - (c) an IgE-mediated disease or disorder selected from the group consisting of urticaria, eczema conjunctivitis, rhinorrhea, rhinitis, particularly allergic rhinitis, gastroenteritis, or a combination thereof;
 - (d) an IgE-mediated disease or disorder selected from the group consisting of myeloma, multiple myeloma, Hodgkin's disease, Hyper-IgE syndrome, Wiskott-Aldrich syndrome, or a combination thereof; and
 - (e) an eosinophilic disease or disorder selected from the group consisting of nodules, eosinophilia, eosinophilic rheumatism, dermatitis and swelling (NERDS).
58. The method of any one of claims 49-57, wherein the administration of said compound or composition is effected by oral administration.
59. The method of claim 58, wherein said compound or composition is administered admixed to food, functional food, drinks or medicinal food.
60. Use of a compound a defined in any one of claims 1-15 or of a composition comprising said compounds for modulation of a Th2 or Th2-like immune response towards a Th1 immune response.

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ISA/EP

61. The use of claim 60 for the prevention, attenuation or treatment of a viral infection and/or virus-induced exacerbations of allergic diseases or disorders such as asthma, chronic obstructive pulmonary disease and autoimmunity.
62. The use of claim 60 for the prevention of development of a Th2 induced inflammatory condition in a tissue or organ of a subject, the method comprising administering an effective amount of a compound of formula (I) as defined in any one of claims 33-40 or of a composition of any one of claims 41-43 to the subject, which compound modulates the number and/or the activation state of dendritic cells (DCs) in the affected tissue or organ, particularly prior to the activation of a T cell response.
63. The use of claim 60, for the treatment of human or animal therapy comprising reducing the release of cytokines from Th2 cells and/or systemic IgE levels, while leaving other antibody isotypes, including IgG2a, IgG2c and IgA, unaffected, and/or the number of eosinophils, and thus treating or preventing an associated disease or disorder such as an allergic disease or disorder, particularly a disease or disorder recited in claim 48, or ameliorating the condition of a patient suffering from such a disease or disorder.

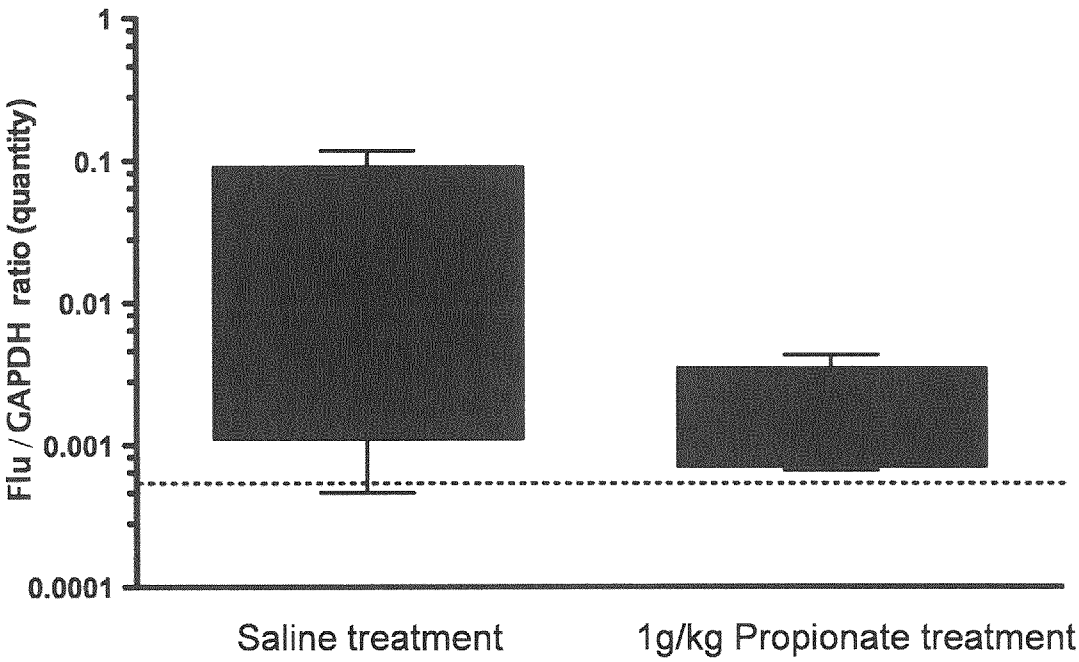


FIGURE 1

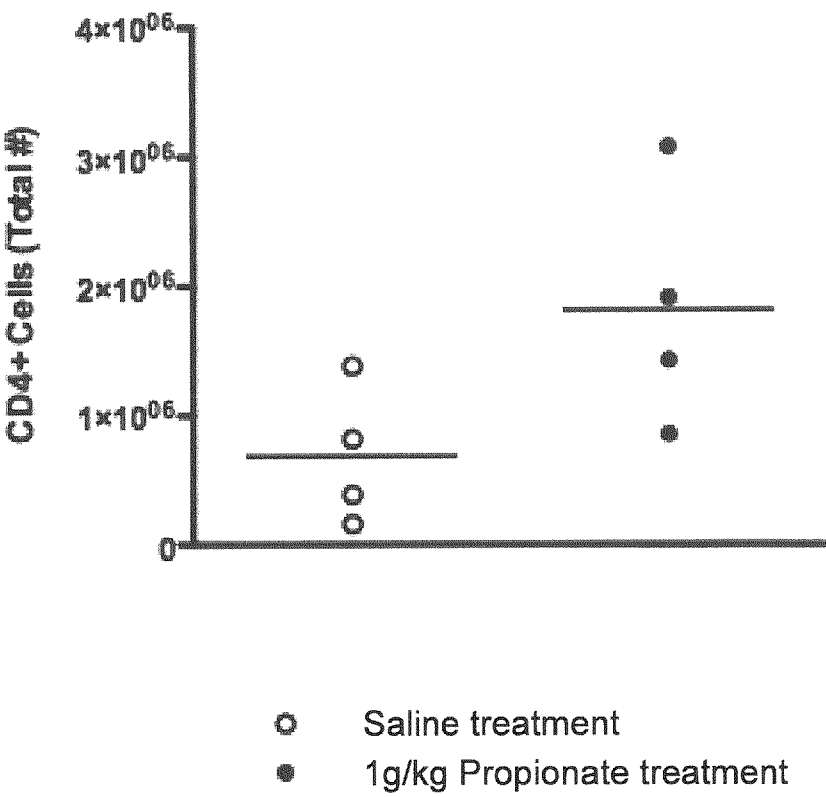


FIGURE 2

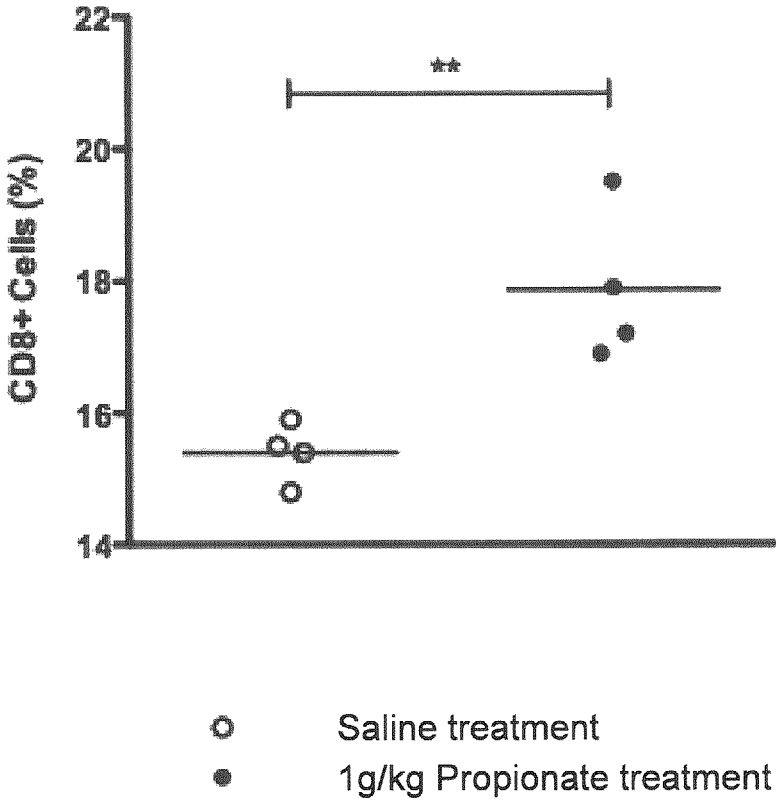


FIGURE 3

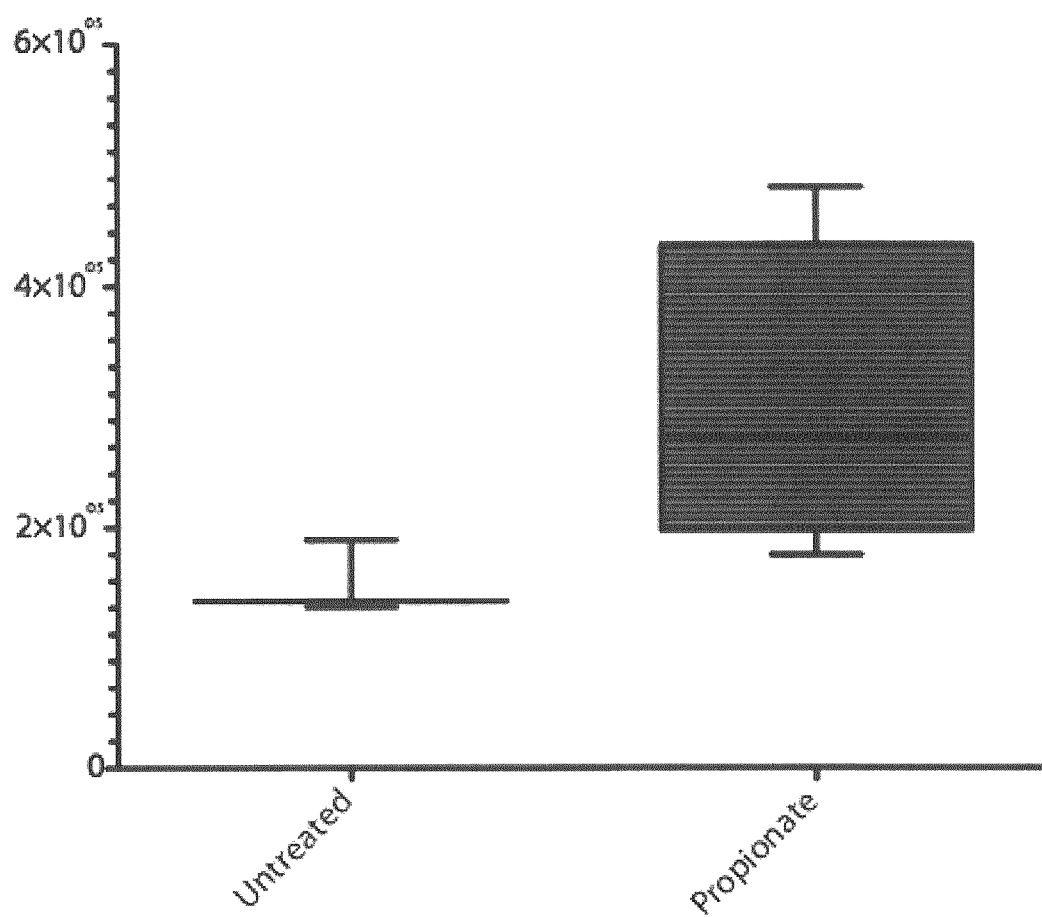


FIGURE 4

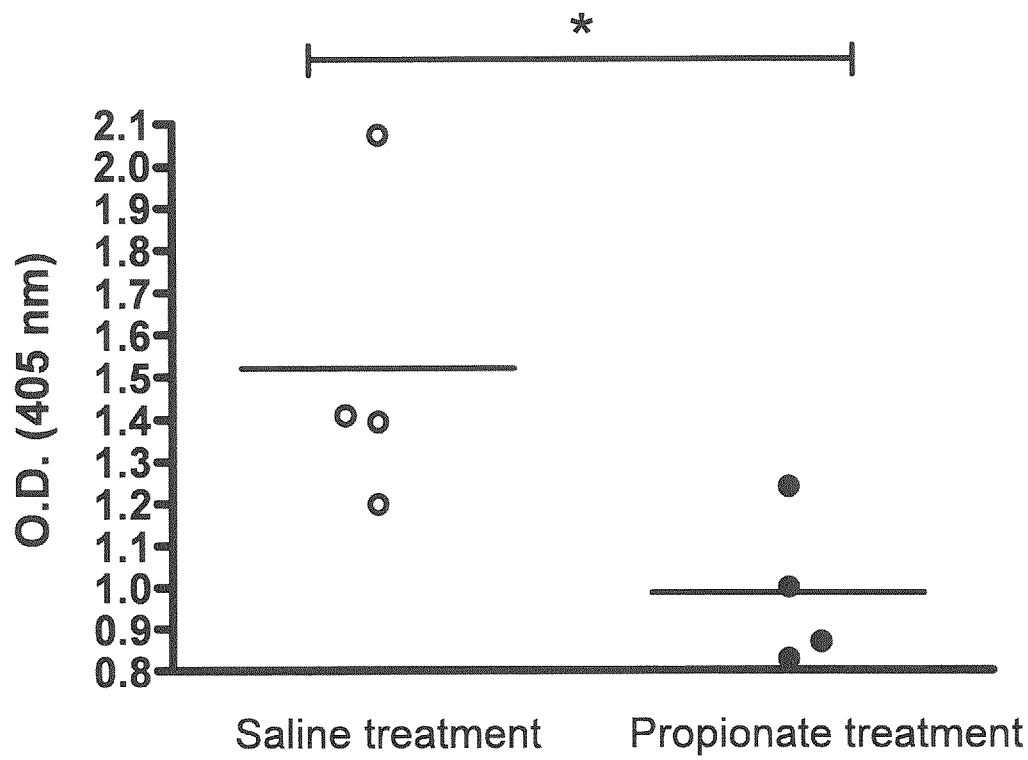


FIGURE 5

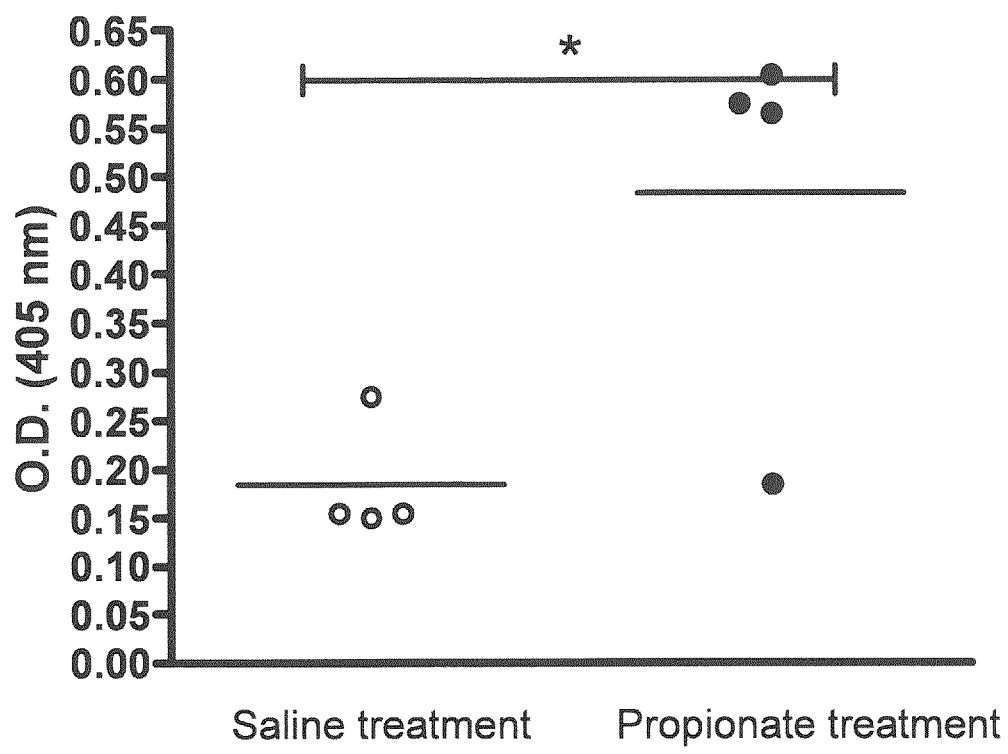


FIGURE 6

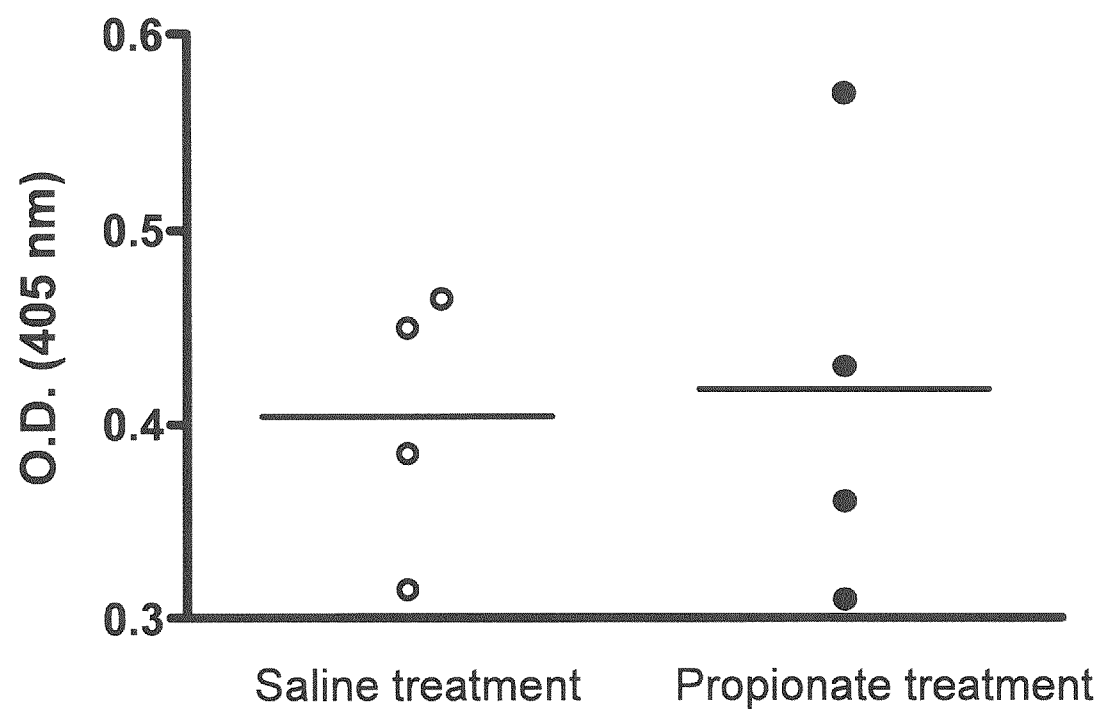


FIGURE 7

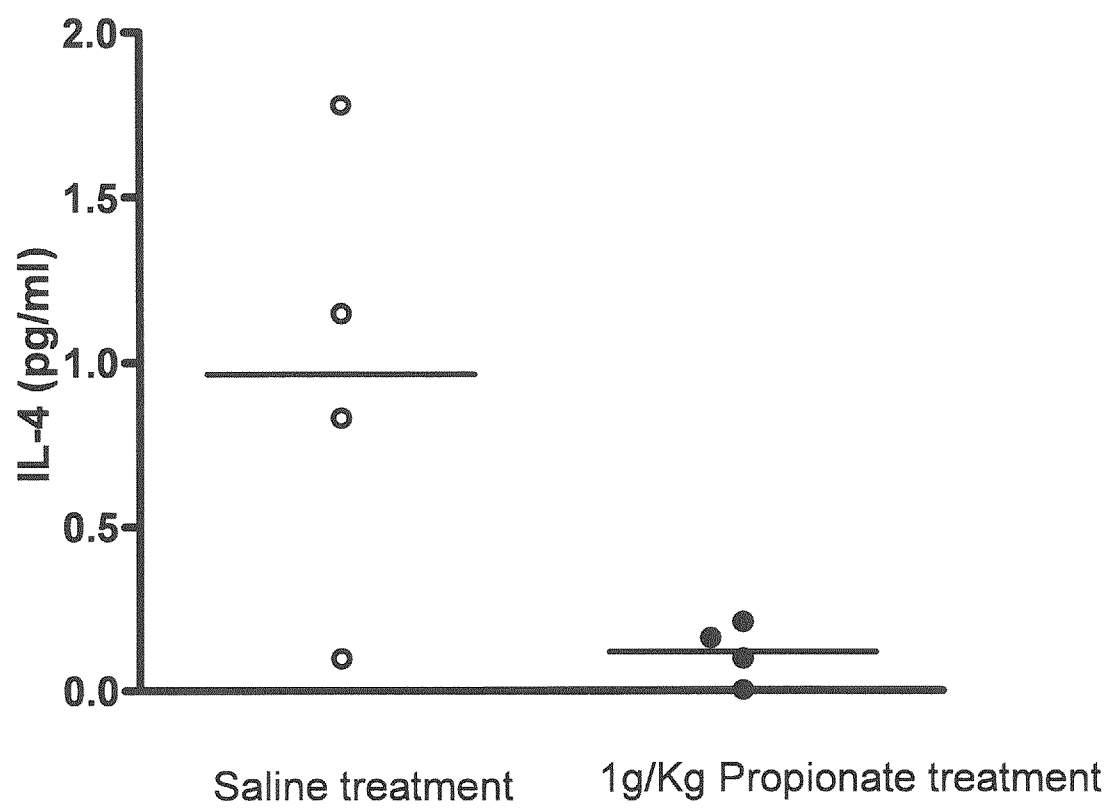


FIGURE 8

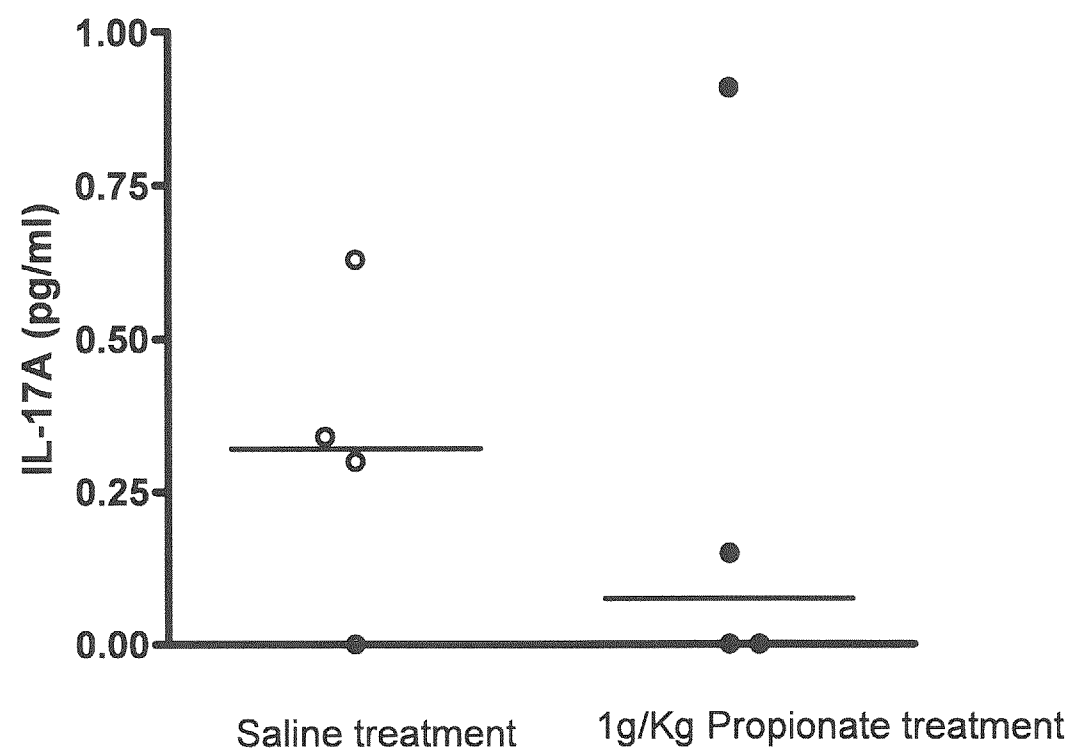


FIGURE 9

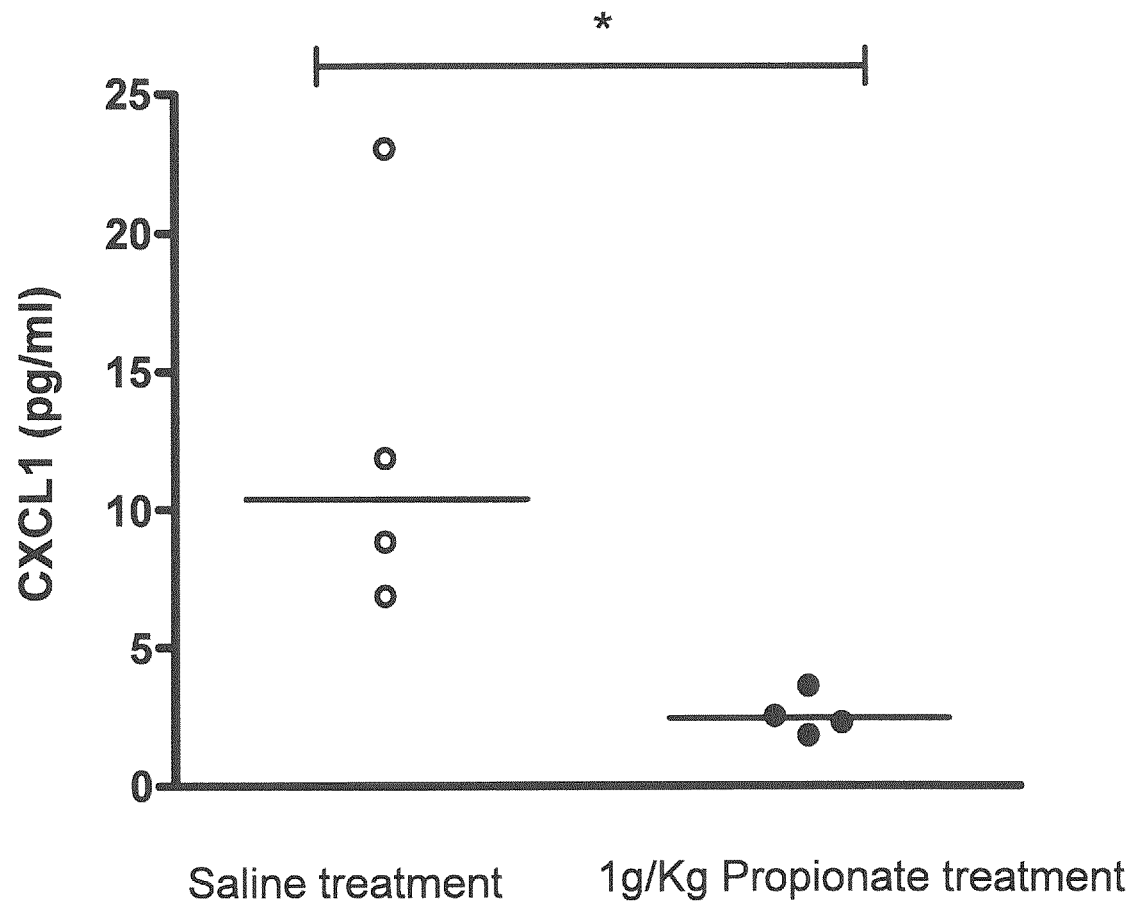


FIGURE 10

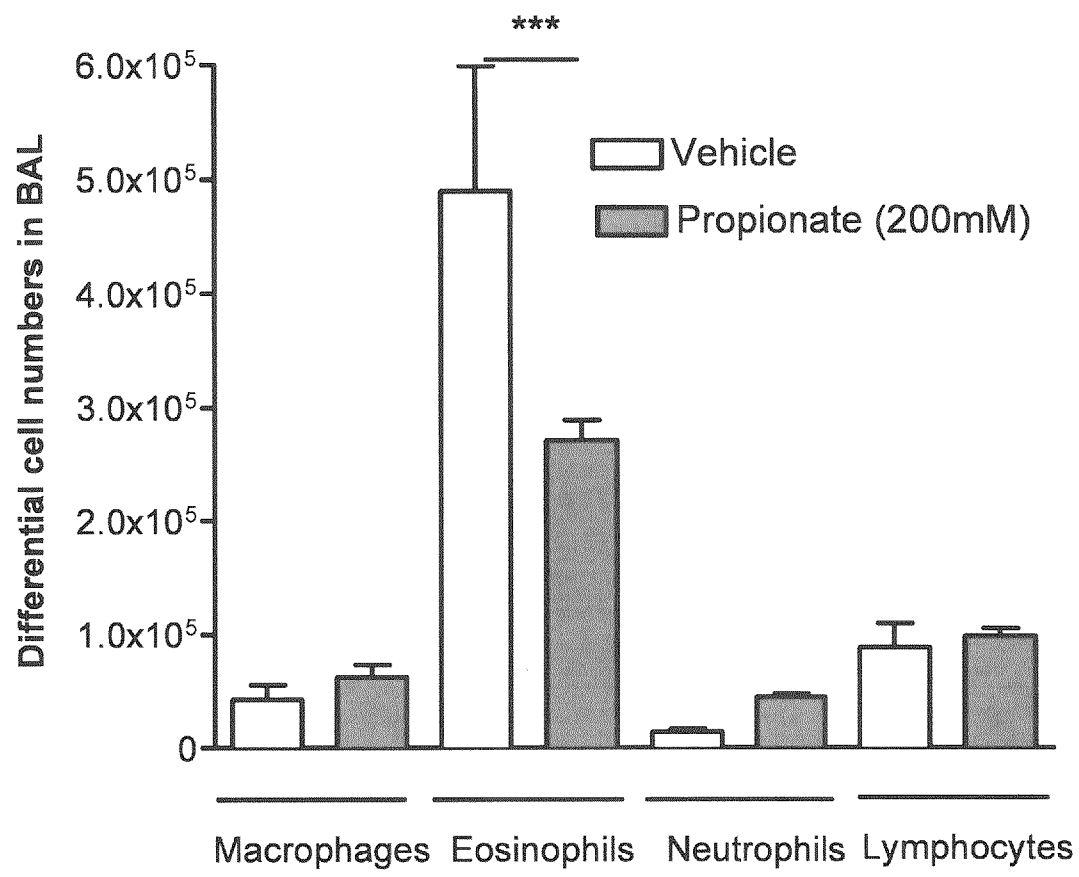


FIGURE 11

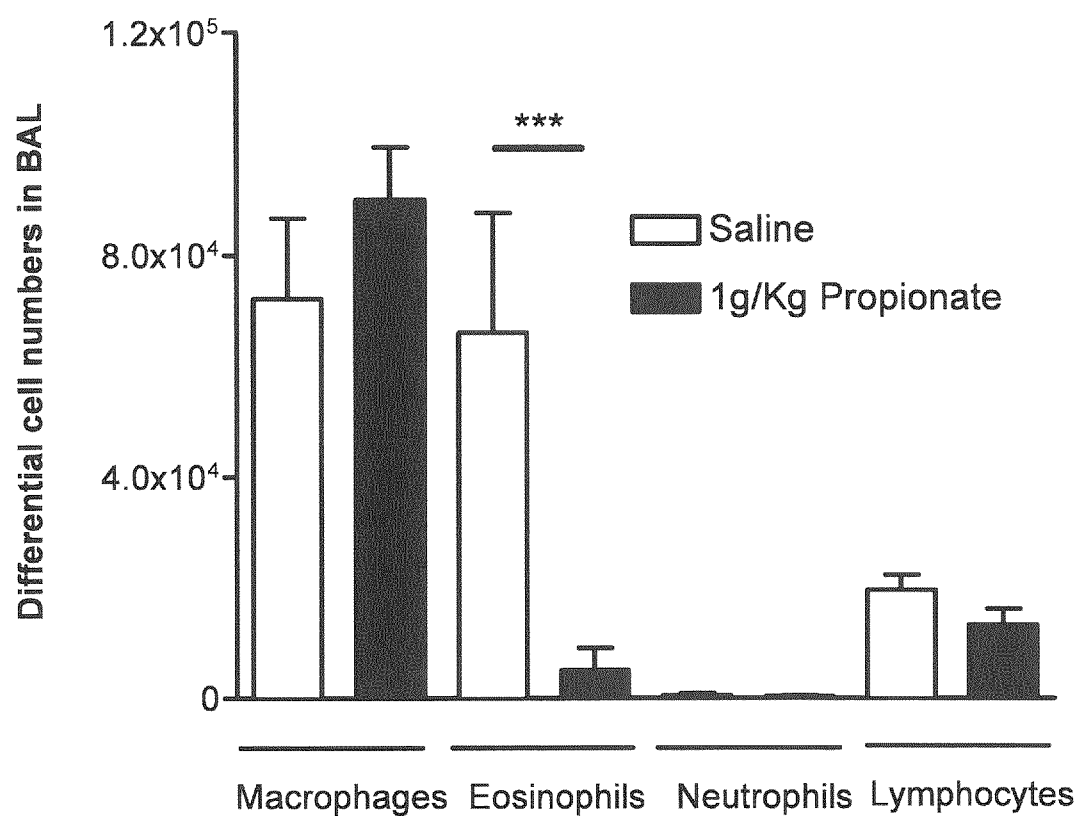


FIGURE 12

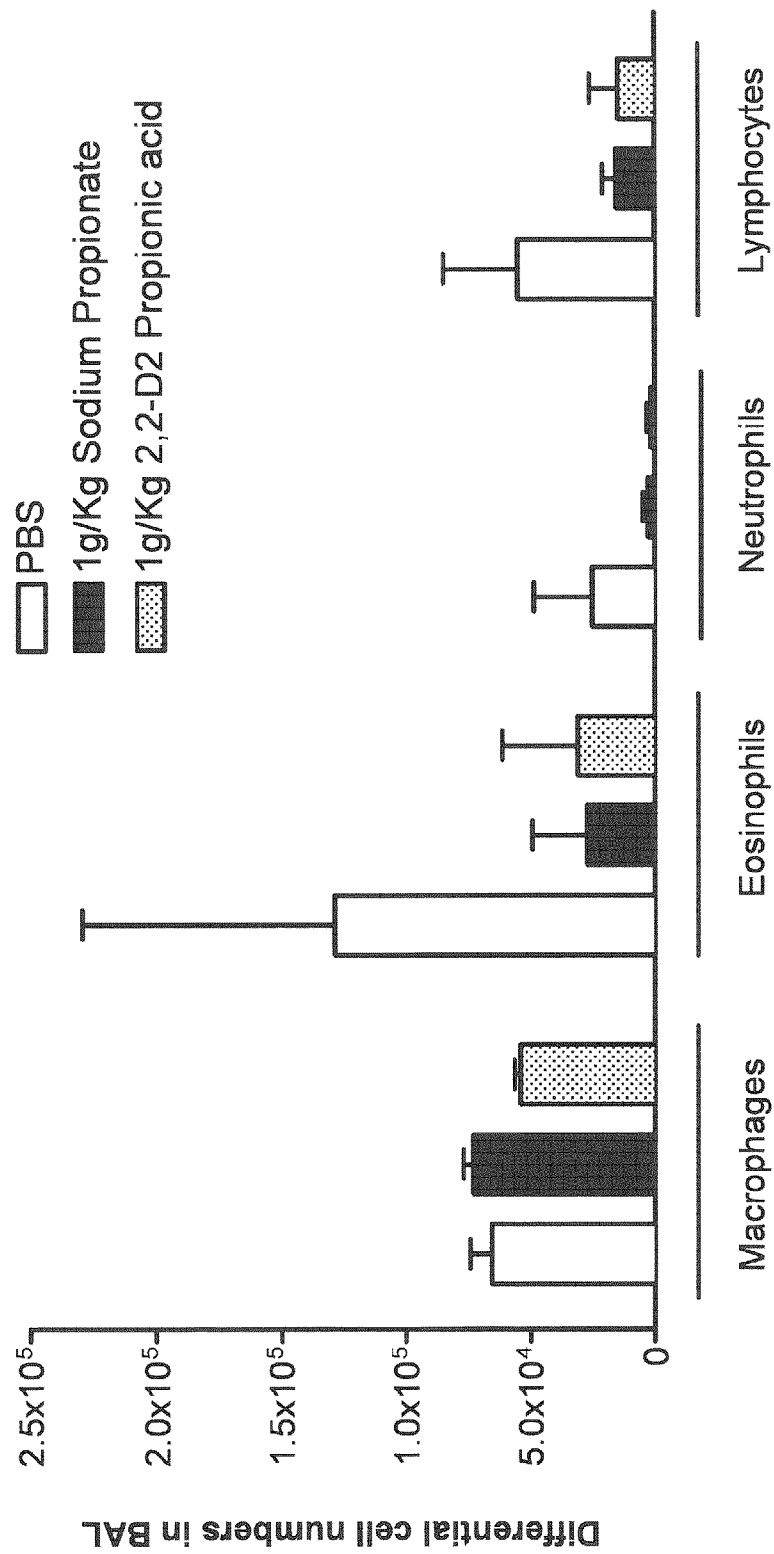


FIGURE 13

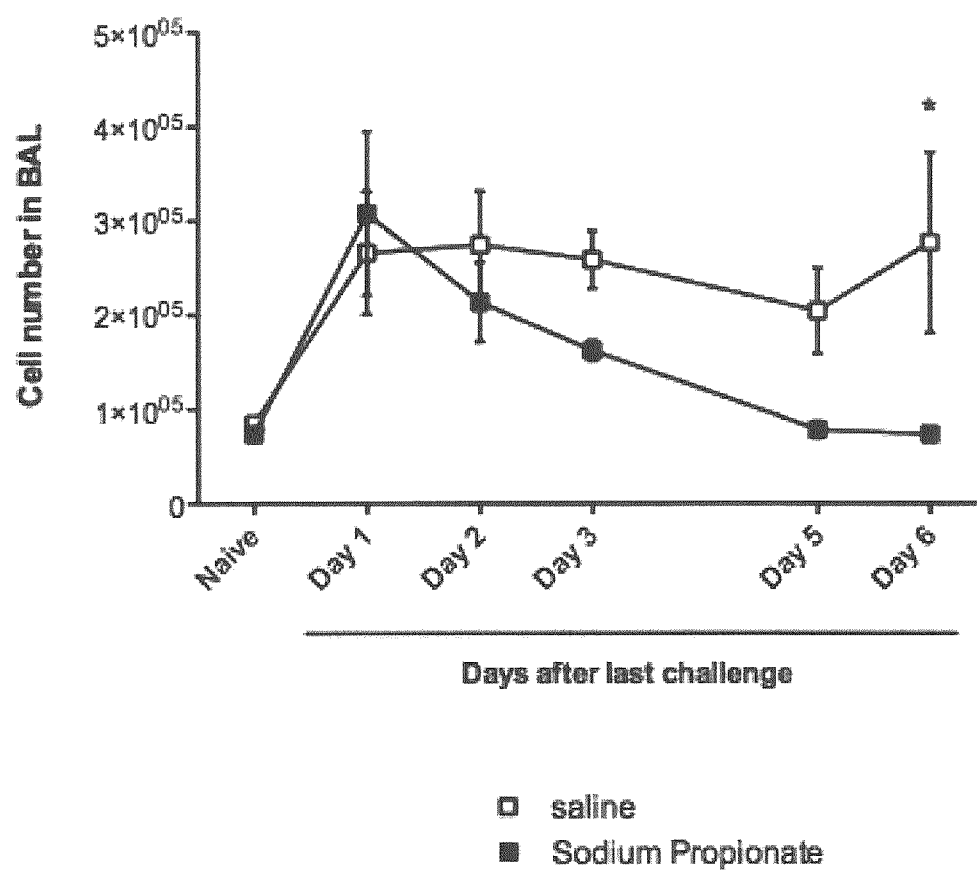


FIGURE 14

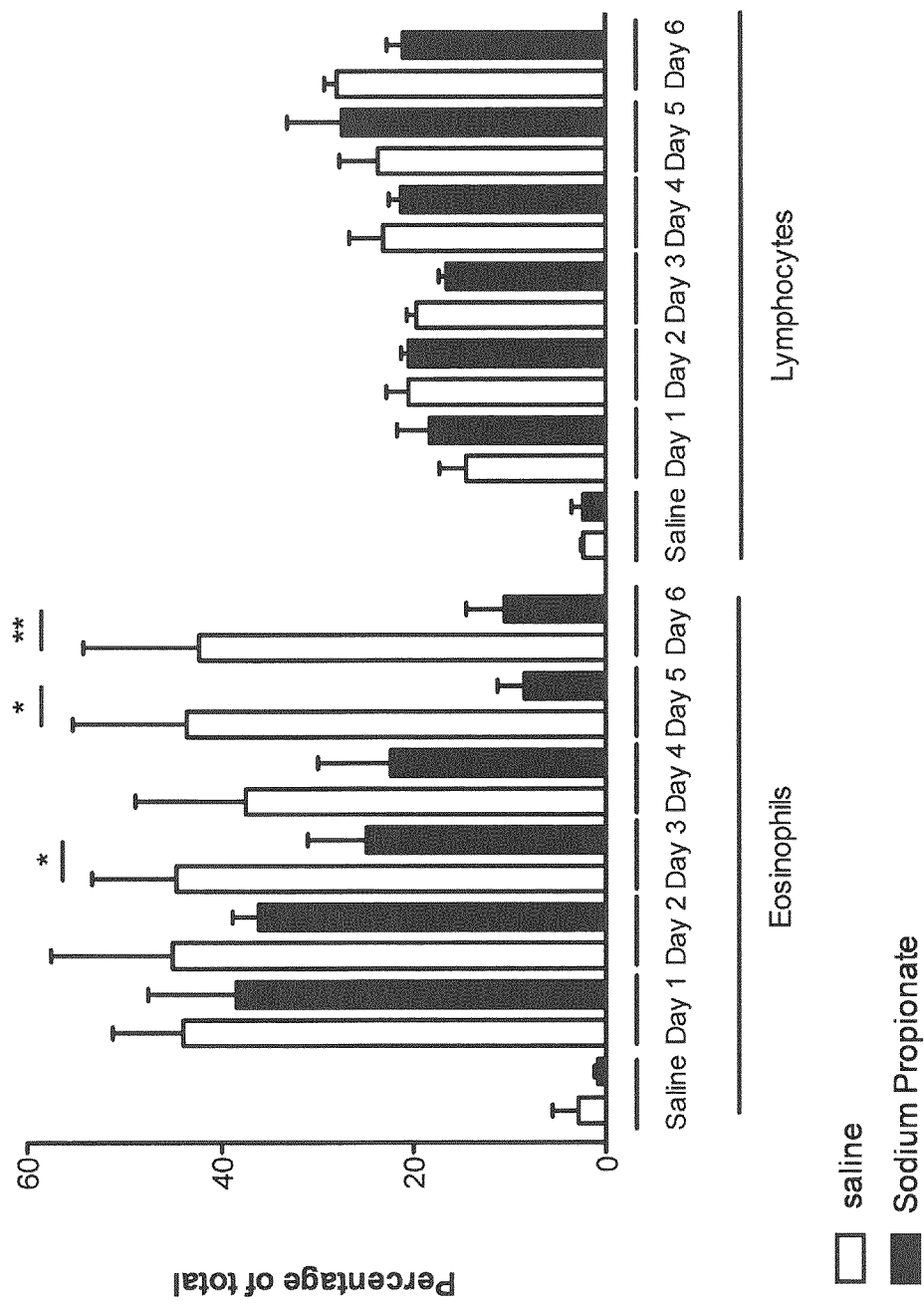


FIGURE 15

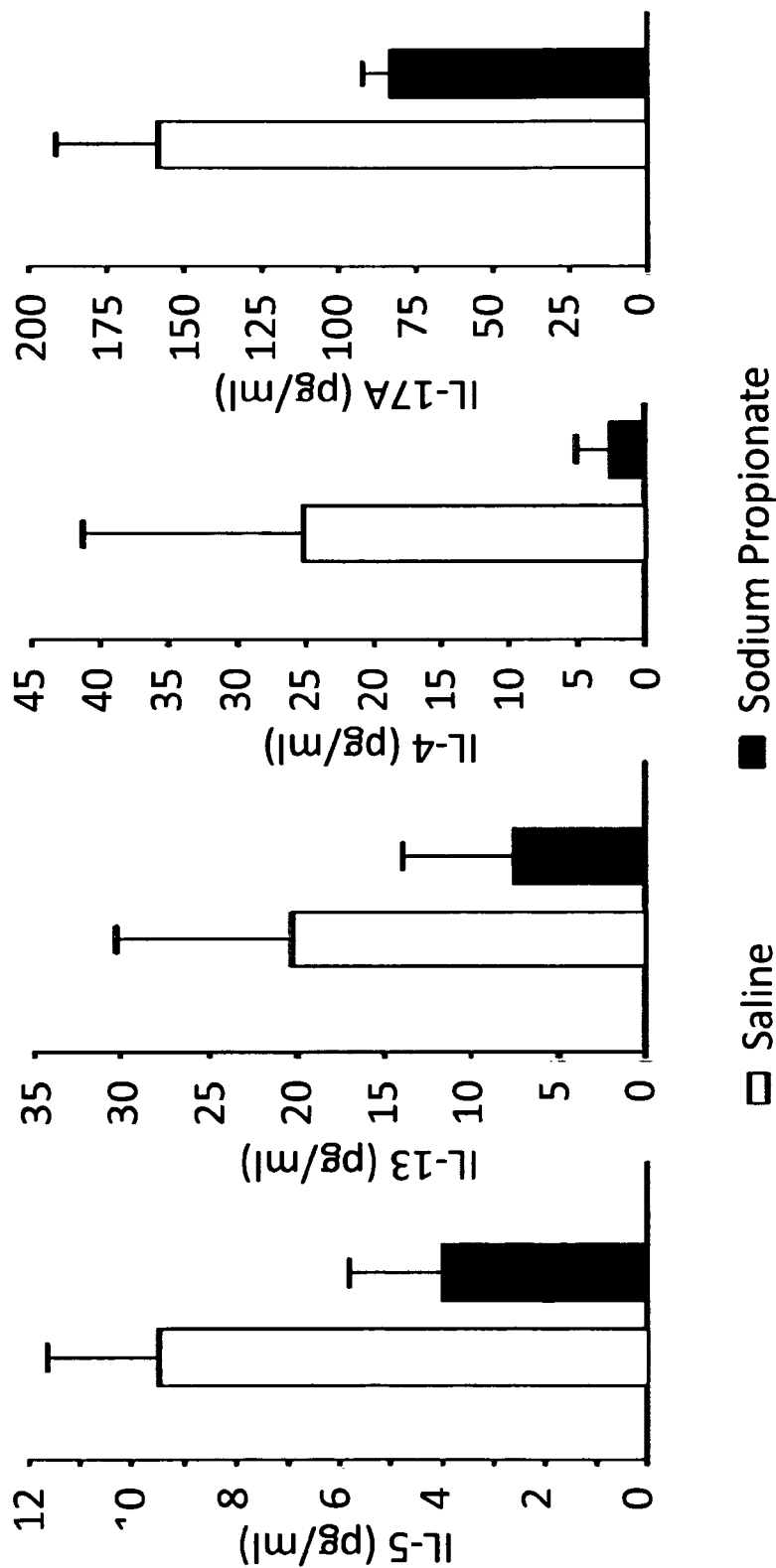


FIGURE 16

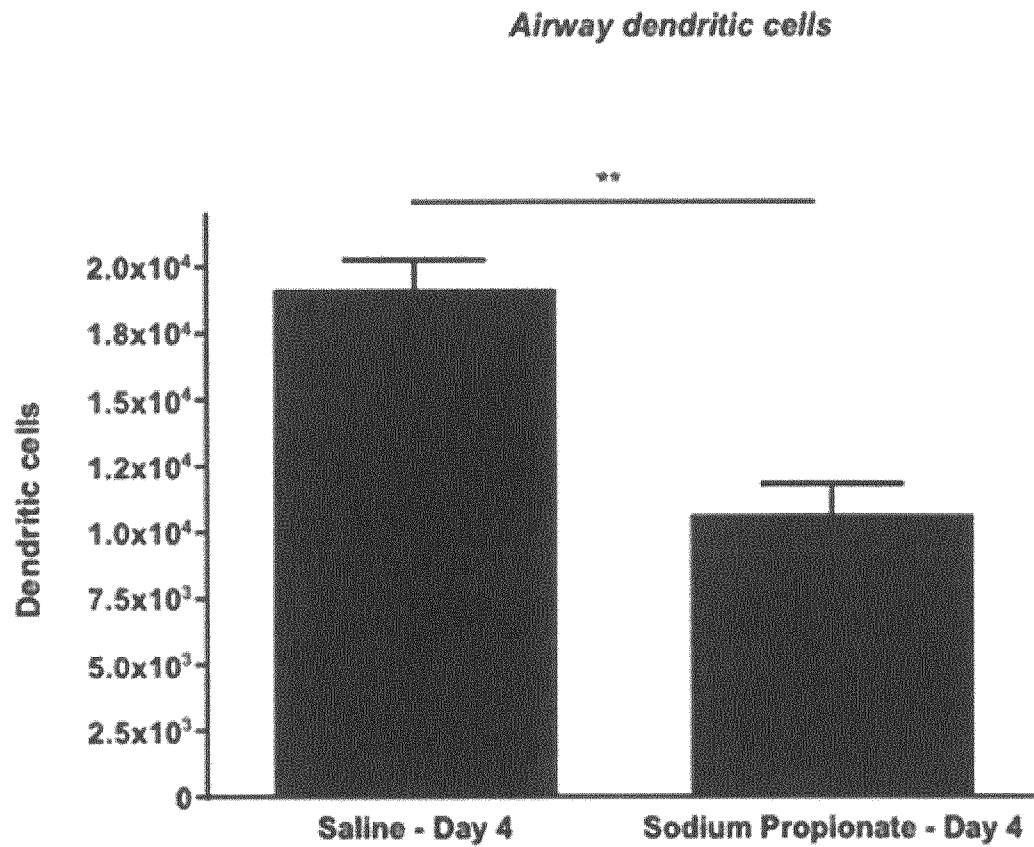


FIGURE 17

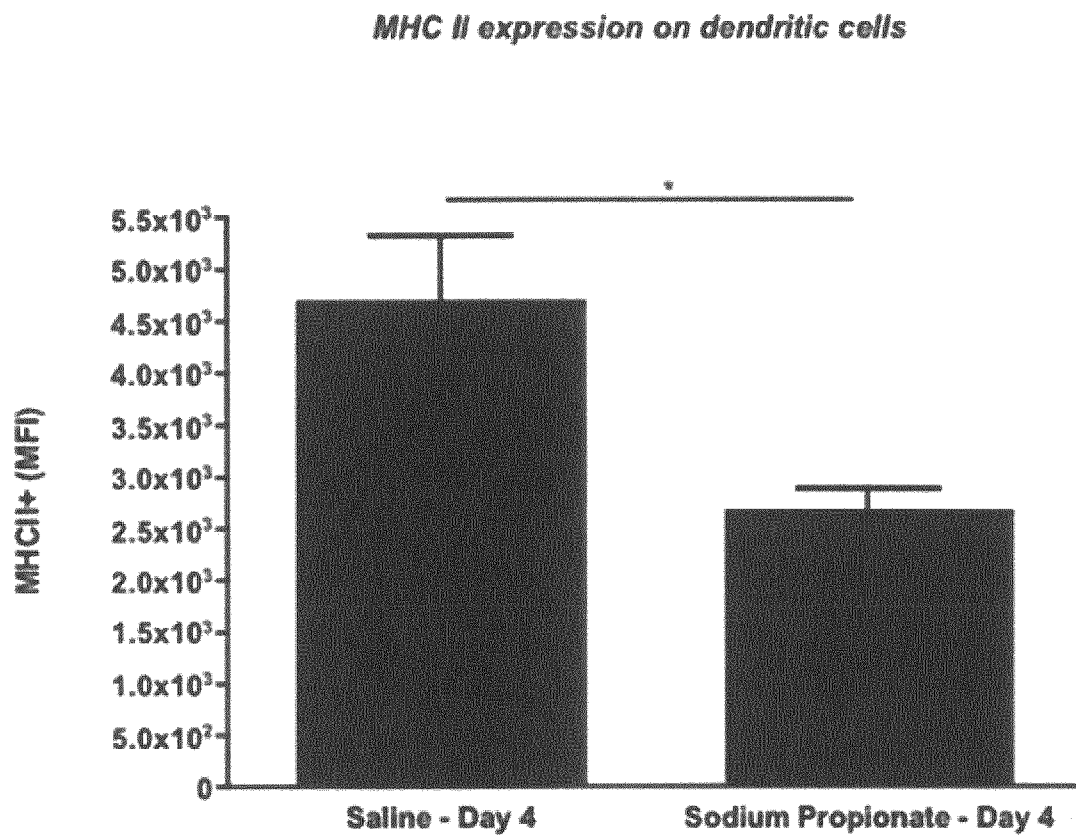
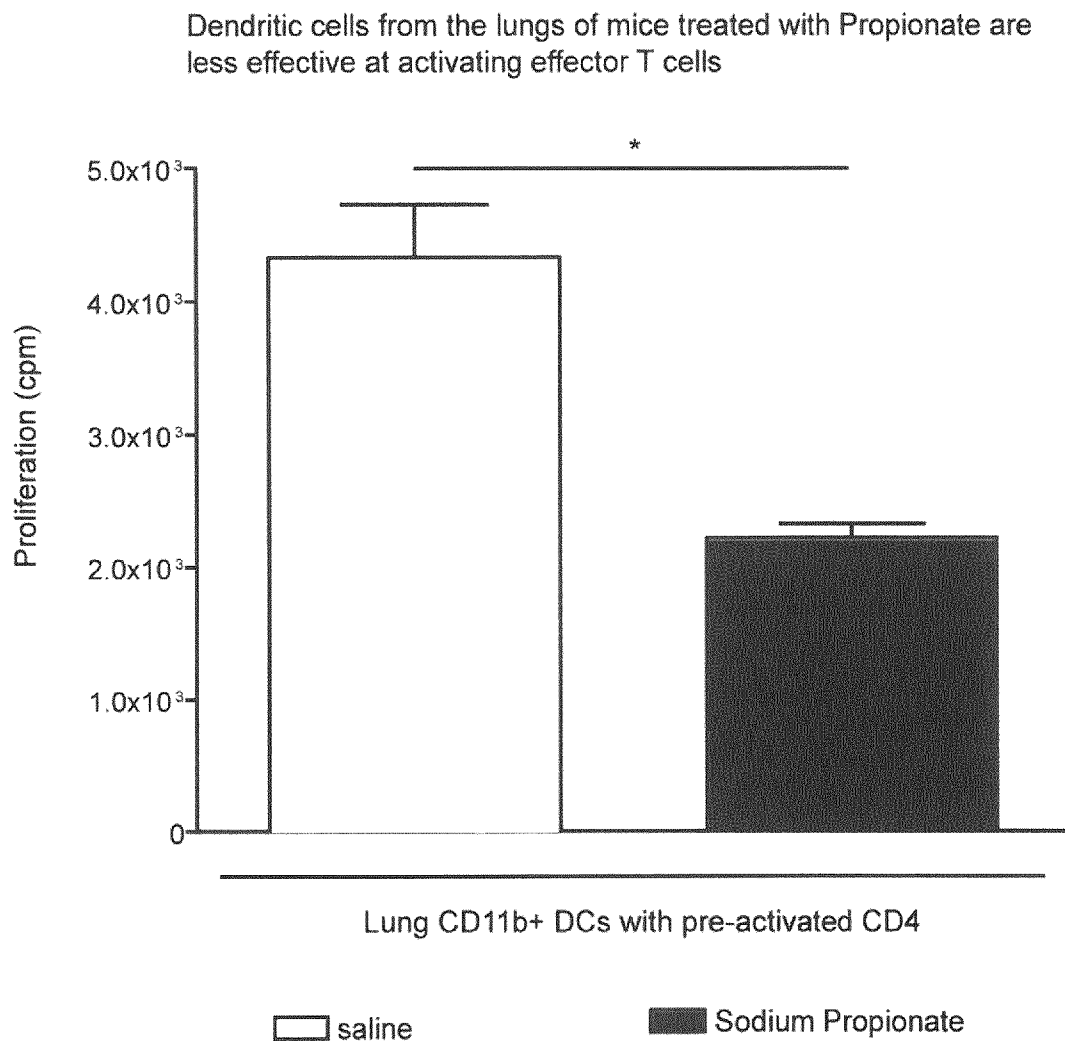


FIGURE 18

**FIGURE 19**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2012/055878

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
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:

see additional sheet

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 an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-10, 14-16, 18-32, 60, 61(all partially)

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

International application No
PCT/EP2012/055878

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/19 A61P11/06 A61P17/00 A61P1/04 A61P37/02 A61P37/08 ADD. 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 A61P Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data											
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%;">Category*</th> <th style="width: 70%;">Citation of document, with indication, where appropriate, of the relevant passages</th> <th style="width: 20%;">Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="vertical-align: top;"> FUKUDA S ET AL: "Immunomodulator e.g. for treating allergosis, autoimmune disease and oral infection disease comprises acetic acid and/or propionic acid as active ingredients", WPI / THOMSON,, vol. 2008, no. 79, 28 August 2008 (2008-08-28), XP002651607, the whole document </td> <td style="vertical-align: top;"> 1-10, 14-16, 18-24, 27-32, 60,61 </td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="vertical-align: top;"> JP 2008 195713 A (SHUNKOSHA KK) 28 August 2008 (2008-08-28) ----- paragraphs [0011], [0016], [0017], [0059] ----- -/-- </td> <td style="vertical-align: top;"> 1-10, 14-16, 18-24, 27-32, 60,61 </td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	FUKUDA S ET AL: "Immunomodulator e.g. for treating allergosis, autoimmune disease and oral infection disease comprises acetic acid and/or propionic acid as active ingredients", WPI / THOMSON,, vol. 2008, no. 79, 28 August 2008 (2008-08-28), XP002651607, the whole document	1-10, 14-16, 18-24, 27-32, 60,61	X	JP 2008 195713 A (SHUNKOSHA KK) 28 August 2008 (2008-08-28) ----- paragraphs [0011], [0016], [0017], [0059] ----- -/--	1-10, 14-16, 18-24, 27-32, 60,61
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.									
X	FUKUDA S ET AL: "Immunomodulator e.g. for treating allergosis, autoimmune disease and oral infection disease comprises acetic acid and/or propionic acid as active ingredients", WPI / THOMSON,, vol. 2008, no. 79, 28 August 2008 (2008-08-28), XP002651607, the whole document	1-10, 14-16, 18-24, 27-32, 60,61									
X	JP 2008 195713 A (SHUNKOSHA KK) 28 August 2008 (2008-08-28) ----- paragraphs [0011], [0016], [0017], [0059] ----- -/--	1-10, 14-16, 18-24, 27-32, 60,61									
☒ 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 13 June 2012		Date of mailing of the international search report 11/09/2012									
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Lemarchand, Aude									

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/055878

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ZHANG Z ET AL: "Valproic acid attenuates inflammation in experimental autoimmune neuritis", CMLS CELLULAR AND MOLECULAR LIFE SCIENCES, BIRKHÄUSER-VERLAG, BA, vol. 65, no. 24, 27 October 2008 (2008-10-27), pages 4055-4065, XP019652181, ISSN: 1420-9071, DOI: DOI:10.1007/S00018-008-8521-4 the whole document	1-10, 14-16, 18-32, 60,61
A	US 4 735 967 A (NEESBY TORBEN E [US]) 5 April 1988 (1988-04-05) the whole document claims 1, 7, 16, 20-21	1-10, 14-16, 18-32, 60,61
X	EP 2 030 616 A1 (ASAN LAB COMPANY CAYMAN LTD [CN]) 4 March 2009 (2009-03-04) pages 3-4, paragraph 16-17; claims 1-3 page 4, lines 4-5	1-10, 14-16, 18-24, 27-32, 60,61
A	FURUHJELM CATRIN ET AL: "Th1 and Th2 chemokines, vaccine-induced immunity, and allergic disease in infants after maternal [omega]-3 fatty acid supplementation during pregnancy and lactation.", PEDIATRIC RESEARCH MAR 2011 LNKD-PUBMED:21099447, vol. 69, no. 3, 1 March 2011 (2011-03-01), pages 259-264, XP007919116, ISSN: 1530-0447 the whole document	21-28
Y	CAVAGLIERI CLAUDIA R ET AL: "Differential effects of short-chain fatty acids on proliferation and production of pro- and anti-inflammatory cytokines by cultured lymphocytes.", LIFE SCIENCES, vol. 73, no. 13, 15 August 2003 (2003-08-15), pages 1683-1690, XP007919115, ISSN: 0024-3205 the whole document	1-10, 14-16, 18-32, 60,61

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/055878

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SHERRY C L ET AL: "Sickness behavior induced by endotoxin can be mitigated by the dietary soluble fiber, pectin, through up-regulation of IL-4 and Th2 polarization", BRAIN, BEHAVIOR AND IMMUNITY, ACADEMIC PRESS, SAN DIEGO, CA, US, vol. 24, no. 4, 1 May 2010 (2010-05-01), pages 631-640, XP027000812, ISSN: 0889-1591 [retrieved on 2010-02-06] page 638, left-hand column, paragraph 1-3 page 631, right-hand column, last paragraph - page 632, left-hand column, paragraph first -----	1-10, 14-16, 18-32, 60,61

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/055878

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 2008195713	A	28-08-2008	NONE
US 4735967	A	05-04-1988	NONE
EP 2030616	A1	04-03-2009	AT 522208 T 15-09-2011
		EP 2030616 A1	04-03-2009
		EP 2033635 A1	11-03-2009
		ES 2371671 T3	09-01-2012
		PL 2033635 T3	31-01-2012
		PT 2033635 E	15-12-2011

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-10, 14-16, 18-32, 60, 61(all partially)

A compound of formula (I) wherein X=0, R= H as defined in claims 5-10 for use in the prevention, attenuation or treatment of a viral infection.

2. claims: 1-10, 14, 15, 17-35, 37-63(all partially)

A compound of formula (I) wherein X=0, R= H as defined in claims 5-10 for use in the prevention, attenuation or treatment of allergic diseases.

3. claims: 1-10, 14, 15, 17-35, 37-63(all partially)

A compound of formula (I) wherein X=0, R= H as defined in claims 5-10 for use in the prevention, attenuation or treatment of asthma or chronic obstructive pulmonary disease.

4. claims: 1-10, 14, 15, 19-35, 37-46, 48-63(all partially)

A compound of formula (I) wherein X=0, R= H as defined in claims 5-10 for use in the prevention, attenuation or treatment of a autoimmune disease.

5. claims: 33-35, 37-60, 62, 63(all partially)

A compound of formula (I) wherein X=0, R= H as defined in claims 5-10 for use in a method for the prevention of development of a Th2 induced inflammatory conditions.

6. claims: 33-35, 37-45, 48-63(all partially)

A compound of formula (I) wherein X=0, R= H as defined in claims 35 or 37 for use in the prevention, attenuation or treatment of an IgE mediated diseases selected from urticaria, eczema conjunctivitis, rhinorrhea, rhinitis, gastroenteritis, myeloma, multiple myeloma, Hodgkin's disease, Hyper-IgE syndrome, Wiskott-Aldrich syndrome.

7. claims: 33-35, 37-44, 46, 48-63(all partially)

A compound of formula (I) wherein X=0, R= H as defined in claims 35 or 37 for use in the treatment of an eosinophilic disease or disorder selected from nodules, eosinophilia, eosinophilic rheumatism, dermatitis and swelling (NERDS).

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

8. claims: 11-13, 36(completely); 1-4, 14, 16-34, 38,
40-63(partially)

A compound of formula (I) wherein X=0, R is not H and is
defined in claims 11-13 or 38 for use in the treatment of
immunogenic disorders.

9. claims: 1-4, 16-34, 40-63(all partially)

A compound of formula (I) as defined in claim 1 not
encompassed by the compounds defined in inventions 1-7 the
for use in the treatment of immunogenic disorders.
