METHODS FOR TREATING ALLERGY AND ENHANCING ALLERGEN-SPECIFIC IMMUNOTHERAPY BY ADMINISTERING AN IL-4R INHIBITOR

FIELD OF THE INVENTION

[0001] The present invention relates to the use of interleukin-4 receptor inhibitors to treat or prevent allergic reactions and to improve the efficacy and/or safety of allergen-specific immunotherapy regimens.

BACKGROUND

[0002] Allergies and allergic diseases are serious medical conditions with consequences ranging from non-life threatening responses that resolve over time to life threatening effects such as anaphylaxis. Allergic reactions can result from contact or exposure to a variety of products such as certain food items, insect venom, plant-derived material (*e.g.*, pollen), chemicals, drugs/medications, and animal dander. Current treatment options for allergies include avoidance, pharmacological symptom treatment and prophylaxis using allergen-specific immunotherapies (SIT). Unfortunately, these current treatment strategies are often inadequate, costly, impractical or involve significant risk. For example, avoidance of allergen is not always possible and can negatively impact on patient and caregiver quality of life. Immunotherapeutic approaches, on the other hand, involve deliberate administration of allergen to susceptible individuals and is therefore inherently risky with the potential for unwanted severe allergic reactions or anaphylaxis. Accordingly, an unmet need exists in the art for novel therapeutic approaches that prevent or treat allergic responses and improve the safety and/or efficacy of immunotherapeutic treatment strategies. .

BRIEF SUMMARY OF THE INVENTION

[0003] According to one aspect of the present invention, methods are provided for treating, preventing or reducing the severity of an allergic reaction in a subject. The methods according to this aspect of the invention comprise administering a therapeutically effective amount of a pharmaceutical composition comprising an interleukin-4 receptor (IL-4R) antagonist to a subject in need thereof. The pharmaceutical composition comprising the IL-4R antagonist may be administered to the subject either before, during or after allergen exposure or manifestation of an allergic symptom.

[0004] According to another aspect of the present invention, methods are provided for enhancing the efficacy and/or safety of an allergen-specific immunotherapy (SIT) regimen. The methods according to this aspect of the invention comprise administering a therapeutically effective amount of a pharmaceutical composition comprising an IL-4R antagonist to a subject in combination with the SIT regimen. According to certain embodiments of this aspect of the invention, the pharmaceutical composition comprising the IL-4R antagonist is administered to

the subject either before the commencement of the SIT regimen or during the course of the SIT regimen. For example, the pharmaceutical composition comprising the IL-4R antagonist may be administered during the up-dosing phase of the SIT regimen and/or during the maintenance phase of the SIT regimen.

[0005] According to another aspect of the present invention, methods are provided for reducing total serum IgE levels in a subject who has been exposed to an allergen. The methods according to this aspect of the invention comprise administering a pharmaceutical composition comprising an IL-4R antagonist to the subject in an amount sufficient to reduce or abrogate IgE production or to reduce or eliminate serum IgE levels in the subject.

[0006] In various embodiments, the pharmaceutical composition comprising the IL-4R antagonist is administered orally, sub-cutaneously, epi-cutaneously or intravenously to a subject in need thereof.

[0007] Exemplary IL-4R antagonists that can be used in the context of the methods of the present invention include, *e.g.*, small molecule chemical inhibitors of IL-4R or its ligands (IL-4 and/or IL-13), or biological agents that target IL-4R or its ligands. According to certain embodiments, the IL-4R antagonist is an antigen-binding protein that binds the IL-4Rα chain and blocks signaling by IL-4, IL-13, or both IL-4 and IL-13. One such type of antigen-binding protein that can be used in the context of the methods of the present invention is an anti-IL-4Rα antibody such as dupilumab.

[0008] Other embodiments of the present invention will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE FIGURES

[0009] **Figure 1, Panel A** depicts the time course of a peanut allergy mouse model in which two doses of an anti-IL-4Rα antibody were administered to the mice. **Panel B** shows the extent of anaphylaxis in three groups of experimental mice, assessed in terms of core temperature decrease over time following IV peanut extract challenge. Mice receiving no antibody are designated with grey filled circles; mice receiving anti-IL-4Rα antibody are designated with black filled squares; mice receiving isotype control antibody are designated with open squares.

[0010] **Figure 2** shows the IgE levels of the three groups of mice referred to in Figure 1 following peanut extract challenge.

[0011] **Figure 3 Panel A** depicts the time course of a peanut allergy mouse model in which a single dose of an anti-IL-4Rα antibody was administered to the mice on Day 13. **Panel B** shows the extent of anaphylaxis in three groups of experimental mice, assessed in terms of core temperature decrease over time following IV peanut extract challenge. Mice receiving no antibody are designated with grey filled circles; mice receiving anti-IL-4Rα antibody are designated with black filled squares; mice receiving isotype control antibody are designated with open squares.

[0012] **Figure 4 Panel A** depicts the time course of a peanut allergy mouse model in which a single dose of an anti-IL-4Rα antibody was administered to the mice on Day 27. **Panel B** shows the extent of anaphylaxis in three groups of experimental mice, assessed in terms of core temperature decrease over time following IV peanut extract challenge. Mice receiving no antibody are designated with grey filled circles; mice receiving anti-IL-4Rα antibody are designated with black filled squares; mice receiving isotype control antibody are designated with open squares.

[0013] **Figure 5** shows the total IgE levels in the three treatment groups of Figures 3 and 4 (no mAb treatment, anti-IL-4Rα treatment, and isotype control-treated mice) on Days 12, 26 and 28 of the respective experimental time courses. **Panel A** shows the results of the experiments in which a single dose of antibody was administered on Day 13; **Panel B** shows the results of the experiments in which a single dose of antibody was administered on Day 27.

[0014] **Figure 6** depicts the time course of a peanut specific immunotherapy mouse model comprising a sensitizing phase, a SIT build-up phase, and a peanut extract challenge. Five antibody injections were administered to the mice on the days indicated.

[0015] **Figure 7** shows the extent of anaphylaxis in three groups of experimental mice subjected to the peanut specific immunotherapy regimen illustrated in Figure 6, as well as a no immunotherapy control group. Results are assessed in terms of core temperature decrease over time following peanut extract challenge. Mice subjected to challenge but receiving no immunotherapy are designated with open circles and dashed lines ("No IT"); mice receiving immunotherapy but no antibody are designated with closed squares and dashed lines ("IT"); mice receiving immunotherapy and isotype control antibody are designated with open squares and dashed lines ("IT + isotype control"); mice receiving immunotherapy and anti-IL-4Rα antibody are designated with closed squares and solid lines ("IT + anti-IL-4Rα).

[0016] **Figures 8, 9, 10 and 11** show the total IgE levels (Figure 8), peanut-specific IgG1 levels (Figure 9), peanut-specific IgG2a levels (Figure 10), and hIgG levels (Figure 11), in three groups of experimental mice subjected to the peanut specific immunotherapy regimen illustrated in Figure 6, as well as a no immunotherapy control group. The various immunoglobulin levels at Day 77 and Day 96 are shown. Mice subjected to challenge but receiving no immunotherapy are designated with closed circles ("No IT"); mice receiving immunotherapy but no antibody are designated with open circles ("IT"); mice receiving immunotherapy and isotype control antibody are designated with closed squares ("IT + isotype control"); mice receiving immunotherapy and anti-IL-4Rα antibody are designated with open squares ("IT + anti-IL-4Rα). Each symbol represents the measured level in an individual mouse.

[0017] **Figure 12** depicts the time course of a variation of the peanut specific immunotherapy mouse model of Figure 6, in which fewer doses (8 versus 12) of peanut extract were administered during the build-up phase as indicated. Five antibody injections were administered to the mice on the days indicated.

[0018] **Figure 13** shows the extent of anaphylaxis in three groups of experimental mice subjected to the peanut specific immunotherapy regimen illustrated in Figure 12, as well as a no immunotherapy control group. Results are assessed in terms of core temperature decrease over time following peanut extract challenge. Treatment groups are the same as in Figure 6.

DETAILED DESCRIPTION

[0019] Before the present invention is described, it is to be understood that this invention is not limited to particular methods and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0020] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. As used herein, the term "about," when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression "about 100" includes 99 and 101 and all values in between (*e.g.*, 99.1, 99.2, 99.3, 99.4, etc.).

[0021] Although any methods and materials similar or equivalent to those described herein can be used in the practice of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to describe in their entirety.

Methods for Treating, Preventing or Reducing the Severity of Allergic Reactions

[0022] The present invention includes methods for treating, preventing or reducing the severity of an allergic reaction in a subject. The methods, according to this aspect of the invention, comprise administering a therapeutically effective amount of a pharmaceutical composition comprising an interleukin-4 receptor (IL-4R) antagonist to a subject in need thereof. As used herein, the terms "treat", "treating", or the like, mean to alleviate symptoms, eliminate the causation of symptoms either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms of an allergic reaction. As used herein, the term "a subject in need thereof" means any human or non-human animal who: (a) is prone to allergic reactions or responses when exposed to one or more allergens; (b) has previously exhibited an allergic response or reaction to one or more allergens; (c) has a known history of allergies; and/or (d) exhibits a sign or symptom of an allergic response or anaphylaxis.

[0023] The present invention also includes methods for reducing total serum IgE levels in a subject who has been exposed to an allergen. The methods according to this aspect of the invention comprise administering a pharmaceutical composition comprising an interleukin-4 receptor (IL-4R) antagonist to the subject in an amount sufficient to reduce or abrogate IgE

production, or to reduce or eliminate serum IgE levels. As used herein, a reduction in serum IgE level means that the amount of IgE measured in the serum of a subject who has been exposed to an allergen and who has been treated with an IL-4R antagonist, is at least 5%, 10%, 20%, 50%, 80%, or 90% lower than the serum IgE level measured in the same or an equivalent subject that has not been treated with the IL-4 antagonist. In certain embodiments, a reduction in serum IgE level means that no or negligible amounts of allergen-specific IgE are detected in the serum of a subject.

[0024] As used herein, the phrases "allergic response," "allergic reaction," "allergic symptom," and the like, include one or more signs or symptoms selected from the group consisting of urticaria (*e.g.*, hives), angioedema, rhinitis, asthma, vomiting, sneezing, runny nose, sinus inflammation, watery eyes, wheezing, bronchospasm, reduced peak expiratory flow (PEF), gastrointestinal distress, flushing, swollen lips, swollen tongue, reduced blood pressure, anaphylaxis, and organ dysfunction/failure. An "allergic response," "allergic reaction," "allergic symptom," etc., also includes immunological responses and reactions such as, *e.g.*, increased IgE production and/or increased allergen-specific immunoglobulin production.

[0025] The term "allergen," as used herein, includes any substance, chemical, particle or composition which is capable of stimulating an allergic response in a susceptible individual. Allergens may be contained within or derived from a food item such as, *e.g.*, dairy products (*e.g.*, cow's milk), egg, celery, sesame, wheat, soy, fish, shellfish, sugars (*e.g.*, sugars present on meat such as alpha-galactose), peanuts, other legumes (*e.g.*, beans, peas, soybeans, etc.), and tree nuts. Alternatively, an allergen may be contained within or derived from a non-food item such as, *e.g.*, dust (*e.g.*, containing dust mite), pollen, insect venom (*e.g.*, venom of bees, wasps, mosquitos, fire ants, etc.), mold, animal fur, animal dander, wool, latex, metals (*e.g.*, nickel), household cleaners, detergents, medication, cosmetics (*e.g.*, perfumes, etc.), drugs (*e.g.*, penicillin, sulfonamides, salicylate, etc.), therapeutic monoclonal antibodies (*e.g.*, cetuximab), ragweed, grass and birch. Exemplary pollen allergens include, *e.g.*, tree pollens such as birch pollen, cedar pollen, oak pollen, alder pollen, hornbeam pollen, aesculus pollen, willow pollen, poplar pollen, plantanus pollen, tilia pollen, olea pollen, Ashe juniper pollen, and *Alstonia scholaris* pollen.

[0026] The methods of the present invention comprise administering a pharmaceutical composition comprising an IL-4R antagonist to a subject before, after and/or during allergen exposure. For example, the present invention includes methods comprising administering a pharmaceutical composition comprising an IL-4R antagonist to a subject less than 12 hours, less than 10 hours, less than 8 hours, less than 6 hours, less than 4 hours, less than 2 hours, less than 1 hour, or less than 30 minutes before allergen exposure. In certain embodiments, the pharmaceutical composition comprising an IL-4R antagonist is administered to a subject several days to weeks prior to allergen exposure (*e.g.*, from about 1 day to about 2 weeks before allergen exposure). The present invention also includes methods comprising administering a

pharmaceutical composition comprising an IL-4R antagonist to a subject less than 12 hours, less than 10 hours, less than 8 hours, less than 6 hours, less than 4 hours, less than 2 hours, less than 1 hour, or less than 30 minutes after allergen exposure. As used herein the expression "allergen exposure" means any incident, episode or occurrence during which a subject ingests, inhales, touches or otherwise is in direct or indirect contact with an allergen.

[0027] The present invention also includes methods comprising administering a pharmaceutical composition comprising an IL-4R antagonist to a subject following the manifestation of one or more allergic symptoms in the subject. For example, the present invention includes methods comprising administering a pharmaceutical composition comprising an IL-4R antagonist to a subject immediately after, 30 minutes after, 1 hour after, 2 hours after, 4 hours after, 6 hours after, 8 hours after, 10 hours after, or 12 hours after the initial manifestation of one or more allergic symptoms in the subject.

[0028] The present invention includes methods for treating, preventing or reducing the severity of an allergic reaction, wherein the allergic reaction is triggered by any of the aforementioned allergens or classes of allergens. For example, the present invention includes methods for treating, preventing or reducing the severity of an allergic reaction triggered by consumption or exposure to a food item (*e.g.*, milk, egg, wheat, soy, fish, shellfish, peanut or tree nut). The present invention also includes methods for treating, preventing or reducing the severity of an allergic reaction triggered by a non-food allergen (*e.g.*, insect venom, dust, mold, animal dander, pollen, latex, medication, ragweed, grass, or birch).

[0029] The present invention includes methods for treating, preventing or reducing the severity of an allergic reaction comprising administering a therapeutically effective amount of a pharmaceutical composition comprising an IL-4R antagonist to a subject in need thereof, wherein the pharmaceutical composition is administered to the subject in multiple doses, *e.g.*, as part of a specific therapeutic dosing regimen. For example, the therapeutic dosing regimen may comprise administering multiple doses of the pharmaceutical composition to the subject at a frequency of about once a day, once every two days, once every three days, once every four days, once every five days, once every six days, once a week, once every two weeks, once every three weeks, once every four weeks, once a month, once every two months, once every three months, once every four months, or less frequently.

[0030] The methods of the present invention, according to certain embodiments, comprise administering to a subject a therapeutically effective amount of a pharmaceutical composition comprising an IL-4R antagonist in combination with a second therapeutic agent. The second therapeutic agent may be an agent selected from the group consisting of, *e.g.*, steroids, antihistamines, decongestants, and anti-IgE agents. As used herein, the phrase "in combination with" means that the pharmaceutical composition comprising an IL-4R antagonist is administered to the subject at the same time as, just before, or just after administration of the second therapeutic agent. In certain embodiments, the second therapeutic agent is

administered as a co-formulation with the IL-4R antagonist. In a related embodiment, the present invention includes methods comprising administering a therapeutically effective amount of a pharmaceutical composition comprising an IL-4R antagonist to a subject who is on a background anti-allergy therapeutic regimen. The background anti-allergy therapeutic regimen may comprise a course of administration of, *e.g.*, steroids, antihistamines, decongestants, anti-IgE agents, etc. The IL-4R antagonist may be added on top of the background anti-allergy therapeutic regimen. In some embodiments, the IL-4R antagonist is added as part of a "background step-down" scheme, wherein the background anti-allergy therapy is gradually withdrawn from the subject over time (*e.g.*, in a stepwise fashion) while the IL-4R antagonist is administered the subject at a constant dose, or at an increasing dose, or at a decreasing dose, over time.

Methods for Enhancing the Efficacy and/or Safety of Allergen-Specific Immunotherapy (SIT)

[0031] The present invention also includes methods for enhancing the efficacy and/or safety of allergen-specific immunotherapy (SIT). The methods according to this aspect of the invention comprise administering a therapeutically effective amount of a pharmaceutical composition comprising an IL-4R antagonist to a subject just prior to or concurrent with a SIT regimen.

[0032] As used herein, the expressions "allergen-specific immunotherapy," "specific immunotherapy," "SIT," "SIT regimen," and the like, refer to the repeated administration of an allergen to a subject over time as means for treating or preventing allergies and allergic reactions, or to reduce or eliminate allergic responses. In a typical SIT regimen, small amounts of allergen are initially administered to an allergic subject, followed by administration of increased amounts of allergen. In certain instances, the SIT regimen comprises at least two consecutive phases: (1) an up-dosing phase, and (2) a maintenance phase. In the up-dosing phase, increasing doses of allergen are administered until an effective and safe dose is achieved. The dose that is established at the end of the up-dosing phase is then administered to the subject throughout the course of the maintenance phase. The duration of the up-dosing phase can be several weeks or several months. In certain embodiments, however, the up-dosing phase is of substantially shorter duration (*e.g.*, less than one week, less than 6 days, less than 5 days, less than 4 days, less than 3 days, or less than 2 days). SIT regimens comprising an up-dosing phase of less than 5 days are sometimes referred to as "Rush" immunotherapy or "Rush SIT." The maintenance phase of an SIT regimen can last several weeks, several months, several years, or indefinitely.

[0033] According to this aspect of the invention, the SIT regimen may comprise administration of a food allergen derived from a food item selected from the group consisting of dairy product, egg, wheat, soy, fish, shellfish, peanut and tree nut. Alternatively, the SIT regimen may

comprise administration of a non-food allergen selected from the group consisting of insect venom, dust, mold, animal dander, pollen, latex, medication, ragweed, grass, and birch.

[0034] According to the methods of the present invention, the IL-4R antagonist can be administered to the subject throughout the entire course of the SIT regimen, or for only a portion of the SIT regimen. For example, the methods of the present invention include administration of a therapeutically effective amount of a pharmaceutical composition comprising an IL-4R antagonist to a subject at a frequency of about once a week, once every two weeks, once every three weeks, once a month, once every two months, once every four months, once every six months, or less frequently, prior to or during the up-dosing phase. In certain embodiments, the pharmaceutical composition comprising an IL-4R antagonist is administered to the subject at a frequency of about once a week, once every two weeks, once every three weeks, once a month, once every two months, once every four months, once every six months, or less frequently, during or after the maintenance phase.

[0035] According to the present invention, the efficacy and/or safety of an SIT regimen is "enhanced" if one or more of the following outcomes or phenomena are observed or achieved in a subject: (1) the duration of the up-dosing phase is decreased without compromising efficacy or safety; (2) the duration of the maintenance phase is decreased without compromising efficacy or safety; (3) the number of doses of allergen administered during the up-dosing or maintenance phase is reduced without compromising efficacy or safety; (4) the frequency of allergen administration during the up-dosing or maintenance phase is reduced without compromising efficacy or safety; (5) the dose of allergen administered during the up-dosing or maintenance phase is increased without compromising efficacy or safety; (6) the frequency of allergic responses or adverse side-effects triggered by the SIT regimen is reduced or eliminated; (7) the use of or need for conventional allergy medications (*e.g.*, steroids, antihistamines, decongestants, anti-IgE agents, etc.) is reduced or eliminated during the up-dosing and/or maintenance phases; (8) the level of allergen-induced IgE expression is reduced; and/or (9) the frequency of anaphylactic reactions is reduced or eliminated. The efficacy of an SIT regimen is also deemed to be "enhanced," according to the present invention, if a subject experiences fewer and/or less severe allergic reactions following SIT therapy in combination with IL-4R blockade than with SIT therapy alone.

[0036] The present invention also includes methods for weaning a subject off of an SIT regimen. The methods according to this aspect of the invention comprise administering to the subject one or more doses of a pharmaceutical composition comprising an IL-4R antagonist, and gradually reducing the frequency and/or quantity of allergen administered to the subject during the course of the SIT regimen. In certain embodiments, the quantity of IL-4R antagonist is increased while the quantity of allergen administered as part of the SIT regimen is decreased. Preferably, administration of the IL-4R antagonist will allow the SIT regimen to be terminated while still providing adequate protection from unwanted allergic reactions.

Interleukin-4 Receptor Antagonists

[0037] The methods of the present invention comprise administering to a subject in need thereof a therapeutic composition comprising an interleukin-4 receptor (IL-4R) antagonist. As used herein, an "IL-4R antagonist" (also referred to herein as an "IL-4Rα antagonist," an "IL-4R blocker," an "IL-4Rα blocker," etc.) is any agent which binds to or interacts with IL-4Rα or an IL-4R ligand, and inhibits or attenuates the normal biological signaling function a type 1 and/or a type 2 IL-4 receptor. Human IL-4Rα has the amino acid sequence of SEQ ID NO: 11. A type 1 IL-4 receptor is a dimeric receptor comprising an IL-4Rα chain and a γc chain. A type 2 IL-4 receptor is a dimeric receptor comprising an IL-4Rα chain and an IL-13Rα1 chain. Type 1 IL-4 receptors interact with and are stimulated by IL-4, while type 2 IL-4 receptors interact with and are stimulated by both IL-4 and IL-13. Thus, the IL-4R antagonists that can be used in the methods of the present invention may function by blocking IL-4-mediated signaling, IL-13-mediated signaling, or both IL-4- and IL-13-mediated signaling. The IL-4R antagonists of the present invention may thus prevent the interaction of IL-4 and/or IL-13 with a type 1 or type 2 receptor.

[0038] Non-limiting examples of categories of IL-4R antagonists include small molecule IL-4R antagonists, anti-IL-4R aptamers, peptide-based IL-4R antagonists (*e.g.*, "peptibody" molecules), "receptor-bodies" (*e.g.*, engineered molecules comprising the ligand-binding domain of an IL-4R component), and antibodies or antigen-binding fragments of antibodies that specifically bind human IL-4Rα. As used herein, IL-4R antagonists also include antigen-binding proteins that specifically bind IL-4 and/or IL-13.

Anti-IL-4Rα Antibodies and Antigen-Binding Fragments Thereof

[0039] According to certain exemplary embodiments of the present invention, the IL-4R antagonist is an anti-IL-4Rα antibody or antigen-binding fragment thereof. The term "antibody," as used herein, includes immunoglobulin molecules comprising four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, as well as multimers thereof (*e.g.*, IgM). In a typical antibody, each heavy chain comprises a heavy chain variable region (abbreviated herein as HCVR or V_H) and a heavy chain constant region. The heavy chain constant region comprises three domains, C_H1, C_H2 and C_H3. Each light chain comprises a light chain variable region (abbreviated herein as LCVR or V_L) and a light chain constant region. The light chain constant region comprises one domain (C_L1). The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. In different embodiments of the invention, the FRs of the anti-IL-4R antibody (or antigen-binding portion thereof) may be identical to the human germline sequences, or may be

naturally or artificially modified. An amino acid consensus sequence may be defined based on a side-by-side analysis of two or more CDRs.

[0040] The term "antibody," as used herein, also includes antigen-binding fragments of full antibody molecules. The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. Antigen-binding fragments of an antibody may be derived, *e.g.*, from full antibody molecules using any suitable standard techniques such as proteolytic digestion or recombinant genetic engineering techniques involving the manipulation and expression of DNA encoding antibody variable and optionally constant domains. Such DNA is known and/or is readily available from, *e.g.*, commercial sources, DNA libraries (including, *e.g.*, phage-antibody libraries), or can be synthesized. The DNA may be sequenced and manipulated chemically or by using molecular biology techniques, for example, to arrange one or more variable and/or constant domains into a suitable configuration, or to introduce codons, create cysteine residues, modify, add or delete amino acids, etc.

[0041] Non-limiting examples of antigen-binding fragments include: (i) Fab fragments; (ii) F(ab')2 fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (*e.g.*, an isolated complementarity determining region (CDR) such as a CDR3 peptide), or a constrained FR3-CDR3-FR4 peptide. Other engineered molecules, such as domain-specific antibodies, single domain antibodies, domain-deleted antibodies, chimeric antibodies, CDR-grafted antibodies, diabodies, triabodies, tetrabodies, minibodies, nanobodies (*e.g.* monovalent nanobodies, bivalent nanobodies, etc.), small modular immunopharmaceuticals (SMIPs), and shark variable IgNAR domains, are also encompassed within the expression "antigen-binding fragment," as used herein.

[0042] An antigen-binding fragment of an antibody will typically comprise at least one variable domain. The variable domain may be of any size or amino acid composition and will generally comprise at least one CDR which is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a V_H domain associated with a V_L domain, the V_H and V_L domains may be situated relative to one another in any suitable arrangement. For example, the variable region may be dimeric and contain V_H-V_H, V_H-V_L or V_L-V_L dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric V_H or V_L domain.

[0043] In certain embodiments, an antigen-binding fragment of an antibody may contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary configurations of variable and constant domains that may be found within an antigen-binding fragment of an antibody of the present invention include: (i) V_H-C_H1; (ii) V_H-C_H2; (iii) V_H-C_H3; (iv) V_H-C_H1-C_H2; (v) V_H-C_H1-C_H2-C_H3; (vi) V_H-C_H2-C_H3; (vii) V_H-C_L; (viii) V_L-C_H1; (ix) V_L-C_H2;

(x) V_L-C_H3; (xi) V_L-C_H1-C_H2; (xii) V_L-C_H1-C_H2-C_H3; (xiii) V_L-C_H2-C_H3; and (xiv) V_L-C_L. In any configuration of variable and constant domains, including any of the exemplary configurations listed above, the variable and constant domains may be either directly linked to one another or may be linked by a full or partial hinge or linker region. A hinge region may consist of at least 2 (*e.g.*, 5, 10, 15, 20, 40, 60 or more) amino acids which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen-binding fragment of an antibody of the present invention may comprise a homo-dimer or hetero-dimer (or other multimer) of any of the variable and constant domain configurations listed above in non-covalent association with one another and/or with one or more monomeric V_H or V_L domain (*e.g.*, by disulfide bond(s)).

[0044] The term "antibody," as used herein, also includes multispecific (*e.g.*, bispecific) antibodies. A multispecific antibody or antigen-binding fragment of an antibody will typically comprise at least two different variable domains, wherein each variable domain is capable of specifically binding to a separate antigen or to a different epitope on the same antigen. Any multispecific antibody format may be adapted for use in the context of an antibody or antigen-binding fragment of an antibody of the present invention using routine techniques available in the art. For example, the present invention includes methods comprising the use of bispecific antibodies wherein one arm of an immunoglobulin is specific for IL-4Rα or a fragment thereof, and the other arm of the immunoglobulin is specific for a second therapeutic target or is conjugated to a therapeutic moiety. Exemplary bispecific formats that can be used in the context of the present invention include, without limitation, *e.g.*, scFv-based or diabody bispecific formats, IgG-scFv fusions, dual variable domain (DVD)-Ig, Quadroma, knobs-into-holes, common light chain (*e.g.*, common light chain with knobs-into-holes, etc.), CrossMab, CrossFab, (SEED)body, leucine zipper, Duobody, IgG1/IgG2, dual acting Fab (DAF)-IgG, and Mab^2 bispecific formats (*see*, *e.g.*, Klein *et al*. 2012, mAbs 4:6, 1-11, and references cited therein, for a review of the foregoing formats). Bispecific antibodies can also be constructed using peptide/nucleic acid conjugation, *e.g.*, wherein unnatural amino acids with orthogonal chemical reactivity are used to generate site-specific antibody-oligonucleotide conjugates which then self-assemble into multimeric complexes with defined composition, valency and geometry. (*See*, *e.g.*, Kazane *et al*., *J. Am. Chem. Soc*. [*Epub*: *Dec. 4, 2012*]).

[0045] The antibodies used in the methods of the present invention may be human antibodies. The term "human antibody," as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human antibodies of the invention may nonetheless include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*), for example in the CDRs and in particular CDR3. However, the term "human antibody," as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species,

such as a mouse, have been grafted onto human framework sequences.

[0046] The antibodies used in the methods of the present invention may be recombinant human antibodies. The term "recombinant human antibody," as used herein, is intended to include all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell (described further below), antibodies isolated from a recombinant, combinatorial human antibody library (described further below), antibodies isolated from an animal (e.g., a mouse) that is transgenic for human immunoglobulin genes (see e.g., Taylor et al. (1992) Nucl. Acids Res. 20:6287-6295) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies are subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the V_H and V_L regions of the recombinant antibodies are sequences that, while derived from and related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

[0047] According to certain embodiments, the antibodies used in the methods of the present invention specifically bind IL-4Rα. The term "specifically binds," or the like, means that an antibody or antigen-binding fragment thereof forms a complex with an antigen that is relatively stable under physiologic conditions. Methods for determining whether an antibody specifically binds to an antigen are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like. For example, an antibody that "specifically binds" IL-4Rα, as used in the context of the present invention, includes antibodies that bind IL-4Rα or portion thereof with a K_D of less than about 1000 nM, less than about 500 nM, less than about 300 nM, less than about 200 nM, less than about 100 nM, less than about 90 nM, less than about 80 nM, less than about 70 nM, less than about 60 nM, less than about 50 nM, less than about 40 nM, less than about 30 nM, less than about 20 nM, less than about 10 nM, less than about 5 nM, less than about 4 nM, less than about 3 nM, less than about 2 nM, less than about 1 nM or less than about 0.5 nM, as measured in a surface plasmon resonance assay. An isolated antibody that specifically binds human IL-4Rα may, however, have cross-reactivity to other antigens, such as IL-4Rα molecules from other (non-human) species.

[0048] According to certain exemplary embodiments of the present invention, the IL-4R antagonist is an anti-IL-4Rα antibody, or antigen-binding fragment thereof comprising a heavy chain variable region (HCVR), light chain variable region (LCVR), and/or complementarity determining regions (CDRs) comprising any of the amino acid sequences of the anti-IL-4R antibodies as set forth in US Patent No. 7,608,693. In certain exemplary embodiments, the anti-IL-4Rα antibody or antigen-binding fragment thereof that can be used in the context of the

methods of the present invention comprises the heavy chain complementarity determining regions (HCDRs) of a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO:1 and the light chain complementarity determining regions (LCDRs) of a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO:2. According to certain embodiments, the anti-IL-4Rα antibody or antigen-binding fragment thereof comprises three HCDRs (HCDR1, HCDR2 and HCDR3) and three LCDRs (LCDR1, LCDR2 and LCDR3), wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO:3; the HCDR2 comprises the amino acid sequence of SEQ ID NO:4; the HCDR3 comprises the amino acid sequence of SEQ ID NO:5; the LCDR1 comprises the amino acid sequence of SEQ ID NO:6; the LCDR2 comprises the amino acid sequence of SEQ ID NO:7; and the LCDR3 comprises the amino acid sequence of SEQ ID NO:8. In yet other embodiments, the anti-IL-4R antibody or antigen-binding fragment thereof comprises an HCVR comprising SEQ ID NO:1 and an LCVR comprising SEQ ID NO:2. According to certain exemplary embodiments, the methods of the present invention comprise the use of the anti-IL-4Rα antibody referred to and known in the art as dupilumab, or a bioequivalent thereof.

[0049] Other anti-IL-4Rα antibodies that can be used in the context of the methods of the present invention include, *e.g.*, the antibody referred to and known in the art as AMG317 (Corren *et al*., 2010, *Am J Respir Crit Care Med., 181*(8):788-796), or any of the anti-IL-4Rα antibodies as set forth in US Patent No. 7,186,809, US Patent No. 7,605,237, US Patent No. 7,608,693, or US Patent No. 8,092,804.

[0050] The anti-IL-4Rα antibodies used in the context of the methods of the present invention may have pH-dependent binding characteristics. For example, an anti-IL-4Rα antibody for use in the methods of the present invention may exhibit reduced binding to IL-4Rα at acidic pH as compared to neutral pH. Alternatively, an anti-IL-4Rα antibody of the invention may exhibit enhanced binding to its antigen at acidic pH as compared to neutral pH. The expression "acidic pH" includes pH values less than about 6.2, *e.g.*, about 6.0, 5.95, 5,9, 5.85, 5.8, 5.75, 5.7, 5.65, 5.6, 5.55, 5.5, 5.45, 5.4, 5.35, 5.3, 5.25, 5.2, 5.15, 5.1, 5.05, 5.0, or less. As used herein, the expression "neutral pH" means a pH of about 7.0 to about 7.4. The expression "neutral pH" includes pH values of about 7.0, 7.05, 7.1, 7.15, 7.2, 7.25, 7.3, 7.35, and 7.4.

[0051] In certain instances, "reduced binding to IL-4Rα at acidic pH as compared to neutral pH" is expressed in terms of a ratio of the K_D value of the antibody binding to IL-4Rα at acidic pH to the K_D value of the antibody binding to IL-4Rα at neutral pH (or vice versa). For example, an antibody or antigen-binding fragment thereof may be regarded as exhibiting "reduced binding to IL-4Rα at acidic pH as compared to neutral pH" for purposes of the present invention if the antibody or antigen-binding fragment thereof exhibits an acidic/neutral K_D ratio of about 3.0 or greater. In certain exemplary embodiments, the acidic/neutral K_D ratio for an antibody or antigen-binding fragment of the present invention can be about 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 10.5, 11.0, 11.5, 12.0, 12.5, 13.0, 13.5, 14.0, 14.5, 15.0,

20.0. 25.0, 30.0, 40.0, 50.0, 60.0, 70.0, 100.0 or greater.

[0052] Antibodies with pH-dependent binding characteristics may be obtained, *e.g.*, by screening a population of antibodies for reduced (or enhanced) binding to a particular antigen at acidic pH as compared to neutral pH. Additionally, modifications of the antigen-binding domain at the amino acid level may yield antibodies with pH-dependent characteristics. For example, by substituting one or more amino acids of an antigen-binding domain (*e.g.*, within a CDR) with a histidine residue, an antibody with reduced antigen-binding at acidic pH relative to neutral pH may be obtained. As used herein, the expression "acidic pH" means a pH of 6.0 or less.

Pharmaceutical Compositions

[0053] The present invention includes methods which comprise administering an IL-4R antagonist to a subject wherein the IL-4R antagonist is contained within a pharmaceutical composition. The pharmaceutical compositions of the invention may be formulated with suitable carriers, excipients, and other agents that provide suitable transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTIN™), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. See also Powell et al. "Compendium of excipients for parenteral formulations" PDA (1998) J Pharm Sci Technol 52:238-311.

[0054] Various delivery systems are known and can be used to administer the pharmaceutical composition of the invention, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the mutant viruses, receptor mediated endocytosis (see, e.g., Wu et al., 1987, J. Biol. Chem. 262:4429-4432). Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The composition may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents.

[0055] A pharmaceutical composition of the present invention can be delivered subcutaneously or intravenously with a standard needle and syringe. In addition, with respect to subcutaneous delivery, a pen delivery device readily has applications in delivering a pharmaceutical composition of the present invention. Such a pen delivery device can be reusable or disposable. A reusable pen delivery device generally utilizes a replaceable cartridge that contains a pharmaceutical composition. Once all of the pharmaceutical composition within the cartridge has been administered and the cartridge is empty, the empty cartridge can readily

be discarded and replaced with a new cartridge that contains the pharmaceutical composition. The pen delivery device can then be reused. In a disposable pen delivery device, there is no replaceable cartridge. Rather, the disposable pen delivery device comes prefilled with the pharmaceutical composition held in a reservoir within the device. Once the reservoir is emptied of the pharmaceutical composition, the entire device is discarded.

[0056] In certain situations, the pharmaceutical composition can be delivered in a controlled release system. In one embodiment, a pump may be used. In another embodiment, polymeric materials can be used; see, Medical Applications of Controlled Release, Langer and Wise (eds.), 1974, CRC Pres., Boca Raton, Florida. In yet another embodiment, a controlled release system can be placed in proximity of the composition's target, thus requiring only a fraction of the systemic dose (see, *e.g.*, Goodson, 1984, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138). Other controlled release systems are discussed in the review by Langer, 1990, Science 249:1527-1533.

[0057] The injectable preparations may include dosage forms for intravenous, subcutaneous, intracutaneous and intramuscular injections, drip infusions, etc. These injectable preparations may be prepared by known methods. For example, the injectable preparations may be prepared, *e.g.*, by dissolving, suspending or emulsifying the antibody or its salt described above in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there are employed, e.g., sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared is preferably filled in an appropriate ampoule.

[0058] Advantageously, the pharmaceutical compositions for oral or parenteral use described above are prepared into dosage forms in a unit dose suited to fit a dose of the active ingredients. Such dosage forms in a unit dose include, for example, tablets, pills, capsules, injections (ampoules), suppositories, etc.

[0059] Exemplary pharmaceutical compositions comprising an anti-IL-4R antibody that can be used in the context of the present invention are disclosed, *e.g.*, in US Patent Application Publication No. 2012/0097565.

Dosage

[0060] The amount of IL-4R antagonist (*e.g.*, anti-IL-4Rα antibody) administered to a subject according to the methods of the present invention is, generally, a therapeutically effective amount. As used herein, the phrase "therapeutically effective amount" means an amount of IL-

4R antagonist that results in one or more of: (a) a reduction in the severity or duration of an allergic reaction; (b) the alleviation of one or more symptoms or indicia of an allergic reaction; (c) prevention or alleviation of anaphylaxis; (d) a reduction in serum IgE level; (e) a reduction in the use or need for conventional allergy therapy (*e.g.*, reduced or eliminated use of antihistamines, decongestants, nasal or inhaled steroids, anti-IgE treatment, epinephrine, etc.); and (f) a reduced frequency of allergic responses to allergen-specific immunotherapy (SIT).

[0061] In the case of an anti-IL-4Rα antibody, a therapeutically effective amount can be from about 0.05 mg to about 600 mg, *e.g.*, about 0.05 mg, about 0.1 mg, about 1.0 mg, about 1.5 mg, about 2.0 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, or about 600 mg, of the anti-IL-4R antibody. In certain embodiments, 300 mg of an anti-IL-4R antibody is administered.

[0062] The amount of IL-4R antagonist contained within the individual doses may be expressed in terms of milligrams of antibody per kilogram of patient body weight (*i.e.*, mg/kg). For example, the IL-4R antagonist may be administered to a patient at a dose of about 0.0001 to about 10 mg/kg of patient body weight.

EXAMPLES

[0063] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1. IL-4R Blockade Prevents Systemic Anaphylaxis in a Mouse Model of Peanut Allergy

[0064] In this Example, the effect of IL-4Rα blockade on peanut-induced anaphylaxis in a mouse model was assessed. An outline of the experimental protocol is shown in Figure 1A. Briefly, three groups of 5 C57BL/6 mice were each sensitized with 100µg of crude peanut

extract and Alum (2mg/ml) administered by subcutaneous injection on Day 0, followed by a boost injection on Day 14. On Day 28 a challenge injection of 50µg of peanut extract was administered intravenously. The first group of mice received no treatment. The second group of mice were administered an anti-mouse IL-4Rα antibody ("anti-mIL-4Rα") subcutaneously at a dose of 25mg/kg on Day 13 and Day 27. The third group of mice received an isotype control antibody on Day 13 and Day 27. The anti-mIL-4Rα antibody used in this and the following Examples was an antibody comprising an HCVR with an amino acid sequence of SEQ ID NO:9 and an LCVR with an amino acid sequence comprising SEQ ID NO:10.

[0065] Systemic anaphylaxis in this model manifests as a drop in core temperature. Therefore, to assess the extent of anaphylaxis in this experimental system, mouse core temperature was measured over the course of 180 minutes following the challenge injection. Results are shown in Figure 1B. Untreated mice and mice receiving isotype control antibody exhibited a rapid decrease in core body temperature at 30 minutes after challenge, indicating an anaphylactic reaction. Core temperature in the control mice gradually increased to baseline by 180 minutes post-challenge. By contrast, mice that received anti-mIL-4Rα treatment exhibited only a slight decrease in core body temperature at 30 minutes post-challenge which returned to normal by the 60 minute time point. The difference in core body temperature change between anti-mIL-4Rα-treated mice and controls at the 30 minute time point was statistically significant ($P<0.0001$).

[0066] The terminal IgE level was also measured for each experimental group (Figure 2). As shown, IL-4Rα blockade significantly decreased total IgE levels below the limit of detection as compared to untreated and isotype control-treated animals.

[0067] The foregoing experiments involved two separate doses of anti-mIL-4Rα antibody (administered on D13 and D27). A second set of experiments was next conducted to assess the effect of a single administration on either Day 13 or Day 27 in the same peanut allergy model. An outline of the experimental protocol is shown in Figure 3A (D13 administration) and Figure 4A (D27 administration). Results are shown in Figures 3B and 4B, respectively. Mice receiving a single administration of anti-mIL-4Rα antibody on Day 13 exhibited significantly less anaphylaxis as compared to untreated and control-treated animals (see Figure 3B), however, the protective effect was not as pronounced as in the two-dose administration experiment (Figure 1B). The protective effect of anti-IL-4Rα treatment was substantially attenuated in the mice receiving single dose of antibody on Day 27 (see Figure 4B).

[0068] In the single administration experiments, IgE levels were measured in samples taken from the animals at Day 12, Day 26 and Day 28. Results are shown in Figure 5A (Day13 administration) and Figure 5B (Day 27 administration). Importantly, the effect of anti-mIL-4Rα antibody on systemic anaphylaxis correlated with the degree of IgE inhibition. The reduction in IgE levels was not immediate following anti-mIL-4Rα treatment but appeared to require about 13 days from the time of antibody administration until the time at which IgE levels were fully

suppressed. This Example therefore supports a role for IL-4R antagonism in preventing allergic reactions.

Example 2: Use of IL-4R Blockade in a Peanut Specific Immunotherapy Model

[0069] The purpose of this Example was to determine the effects of IL-4Rα blockade when added to an allergen-specific immunotherapy (SIT) regimen. For these experiments, a mouse peanut specific immunotherapy model was developed based in part on the model of Kulis *et al.*, *J. Allergy Clin. Immunol. 127*(1):81-88 (2011). Two sets of experiments were conducted, as described below.

[0070] An outline of the experimental protocol used in the first set of experiments is shown in Figure 6. Four groups of mice were used in these experiments. Three of the four groups of mice were subjected to a peanut specific immunotherapy regimen comprising a Sensitization Phase, a Build-up Phase, and a Challenge. The Sensitization Phase consisted of administration of 0.5mg peanut extract + 2mg Alum administered intraperitoneally on Days 0, 7 and 28. The Build-up Phase consisted of twelve separate administrations of various doses of peanut extract without Alum on Days 49, 51, 53, 56, 58, 60, 63, 65, 67, 70, 72 and 74. The Challenge consisted of administration of 1 mg of peanut extract on Day 98.

[0071] The various treatment groups for these experiments were as follows: Group A received no immunotherapy and no antibody ("No IT"); Group B received immunotherapy only, without antibody ("IT"); Group C received immunotherapy plus isotype control antibody on Days 36, 50, 57, 64 and 71 ("IT + isotype control"); and Group D received immunotherapy plus anti-mIL-4Rα antibody (25mg/kg, subcutaneous) on Days 36, 50, 57, 64 and 71 ("IT + anti-IL-4Rα"). The anti-mIL-4Rα antibody used in these experiments was the same antibody as used in Example 1, herein.

[0072] To assess the extent of anaphylaxis in this system, mouse core temperature was measured over the course of 180 minutes following the challenge injection. In addition, serum samples were collected throughout the experiment (at Days 35, 46, 77 and 98) for immunoglobulin measurements. Anaphylaxis results are shown in Figure 7. Total IgE, IgG1, IgG2a and IgG levels at Days 77 and 96 are shown in Figures 8, 9, 10 and 11, respectively.

[0073] The results of these experiments show that allergen-specific immunotherapy by itself protects against peanut-induced systemic anaphylaxis in this model (see Figure 7). Importantly, administration of an anti-IL-4Rα antibody did not interfere with the observed protective effects of SIT. In addition, a trend towards increased IgE induced by SIT was observed in IT-only and IT + isotype control treated animals. By contrast, IgE production was blocked in anti-IL-4Rα-treated animals (see Figure 8). A tendency toward increased peanut-specific IgG1 titers was observed in animals treated with immunotherapy (with or without antibody treatment), however statistical significance was only observed in the IT animals at Day 77 (see Figure 9). IL-4Rα blockade was also observed to cause an increase in peanut-specific IgG2a (see Figure 10). The results from

this first set of experiments provide experimental support for the use of IL-4R blockade as a means to potentially improve the efficacy and safety of allergen-specific immunotherapy.

[0074] A second set of experiments was next conducted to determine the effect of IL-4R blockade in a SIT regimen with fewer allergen doses during the Build-up Phase. An outline of the experimental protocol used in this second set of experiments is shown in Figure 12. As before, four groups of mice were used in these experiments. Three of the four groups of mice were subjected to a peanut specific immunotherapy regimen identical to the regimen used in the first set of experiments except that fewer doses of allergen were administered during the Build-up Phase. In particular, the Build-up Phase in these experiments consisted of only eight (as opposed to twelve) separate administrations of various doses of peanut extract without Alum on Days 51 and 53 (0.1 mg), 58 and 60 (0.25 mg), 65 and 67 (0.5 mg), and 72 and 74 (0.5 mg).

[0075] Again, four treatment groups were used ("No IT", "IT only", "IT + isotype control"; and "IT + anti-IL-4Rα"). Antibody was administered at the same dose as before (25 mg/kg SQ), however injections were administered on Days 36, 49, 56, 63 and 70 (as opposed to Days 36, 50, 57, 64 and 71 in the first set of experiments). The extent of anaphylaxis was determined by measuring mouse core temperature over the course of 240 minutes following the challenge injection. Results are shown in Figure 13.

[0076] In these experiments, less frequent allergen administration during the Build-up Phase was less protective against anaphylaxis as compared to the more frequent dosing regimen used in the first set of experiments (8 doses versus 12). In particular, a substantial drop in core body temperature in the IT and IT + isotype control mice during the first 60 minutes after allergen Challenge was observed which was only slightly less severe than what was observed in the "No IT" mice. By contrast, only a mild anaphylactic response (*i.e.*, slight decrease in core body temperature) was observed in the anti-IL-4Rα-treated mice. The Build-up Phase in this model may be considered analogous to the maintenance phase in conventional SIT regimens in humans. The results from this Example therefore indicate that IL-4R blockade can substantially improve the safety of allergen-specific immunotherapy regimens by allowing for reduced maintenance phase dosing. Less frequent allergen dosing would also be more convenient and would result in greater patient compliance in SIT regimens.

[0077] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

What is claimed is:

1. Use of an interleukin-4 receptor (IL-4R) antagonist wherein the IL-4R antagonist is an antibody or antigen-binding fragment thereof that binds IL-4Ra and prevents the interaction of IL-4 and/or IL-13 with a type 1 or type 2 IL-4 receptor for the production of a medicament for treating, preventing or reducing the severity of an allergic reaction triggered by consumption of or exposure to a non-food item by a subject, wherein the antibody or antigen-binding fragment thereof comprises three HCDRs (HCDR1, HCDR2 and HCDR3) and three LCDRs (LCDR1, LCDR2 and LCDR3), wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO:3, the HCDR2 comprises the amino acid sequence of SEQ ID NO:4, the HCDR3 comprises the amino acid sequence of SEQ ID NO:5, the LCDR1 comprises the amino acid sequence of SEQ ID NO:6, the LCDR2 comprises the amino acid sequence of SEQ ID NO:7, and the LCDR3 comprises the amino acid sequence of SEQ ID NO:8.

2. Use of an interleukin-4 receptor (IL-4R) antagonist wherein the IL-4R antagonist is an antibody or antigen-binding fragment thereof that binds IL-4Ra and prevents the interaction of IL-4 and/or IL-13 with a type 1 or type 2 IL-4 receptor for the production of a medicament for enhancing the efficacy and/or safety of an allergen-specific immunotherapy (SIT) regimen wherein the SIT regimen comprises administration of a non-food allergen derived from a non-food item selected from the group consisting of dust, pollen, insect venom, mold, animal fur, animal dander, wool, latex, metals, household cleaners, detergents, drugs, therapeutic monoclonal antibodies, ragweed, grass and birch, wherein the antibody or antigen-binding fragment thereof comprises three HCDRs (HCDR1, HCDR2 and HCDR3) and three LCDRs (LCDR1, LCDR2 and LCDR3), wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO:3, the HCDR2 comprises the amino acid sequence of SEQ ID NO:4, the HCDR3 comprises the amino acid sequence of SEQ ID NO:5, the LCDR1 comprises the amino acid sequence of SEQ ID NO:6, the LCDR2 comprises the amino acid sequence of SEQ ID NO:7, and the LCDR3 comprises the amino acid sequence of SEQ ID NO:8, and wherein the antibody or antigen-binding fragment thereof is formulated in a medicament for administration to a subject prior to or concurrent with the SIT regimen.

3. Use of an interleukin-4 receptor (IL-4R) antagonist wherein the IL-4R antagonist is an antibody or antigen-binding fragment thereof that binds IL-4Ra and prevents the interaction of IL-4 and/or IL-13 with a type 1 or type 2 IL-4 receptor for the production of a medicament for reducing total serum IgE levels in a subject who has been exposed to an

allergen wherein the allergen is a non-food allergen derived from or contained within a non-food item selected from the group consisting of dust, pollen, insect venom, mold, animal fur, animal dander, wool, latex, metals, household cleaners, detergents, drugs, therapeutic monoclonal antibodies, ragweed, grass and birch, wherein the antibody or antigen-binding fragment thereof comprises three HCDRs (HCDR1, HCDR2 and HCDR3) and three LCDRs (LCDR1, LCDR2 and LCDR3), wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO:3, the HCDR2 comprises the amino acid sequence of SEQ ID NO:4, the HCDR3 comprises the amino acid sequence of SEQ ID NO:5, the LCDR1 comprises the amino acid sequence of SEQ ID NO:6, the LCDR2 comprises the amino acid sequence of SEQ ID NO:7, and the LCDR3 comprises the amino acid sequence of SEQ ID NO:8, and wherein said antibody or antigen-binding fragment thereof is formulated in a medicament for administration to the subject in an amount sufficient to reduce or abrogate IgE production.

4. The use according to any one of claims 1 to 3, wherein the HCVR comprises the amino acid sequence of SEQ ID NO: 1 and the LCVR comprises the amino acid sequence of SEQ ID NO: 2.

5. The use according to any one of claims 1 to 4, wherein the IL-4R antagonist is dupilumab.

6. The use according to any one of claims 1, 4 and 5, wherein the antibody or antigen-binding fragment thereof is formulated in a medicament for administration to the subject before non-food allergen exposure.

7. The use according to any one of claims 1, 4 and 5, wherein the antibody or antigen-binding fragment thereof is formulated in a medicament for administration to the subject less than 4 hours before non-food allergen exposure.

8. The use according to any one of claims 1, 4 and 5, wherein the antibody or antigen-binding fragment thereof is formulated in a medicament for administration to the subject during or after non-food allergen exposure.

9. The use according to any one of claims 1, 4 to 8, wherein the antibody or antigen-binding fragment thereof is formulated in a medicament for administration to the subject less than 4 hours after non-food allergen exposure.

10. The use according to any one of claims 1, 4 to 8,, wherein the antibody or antigen-binding fragment thereof is formulated in a medicament for administration to the subject following the manifestation of one or more allergic symptoms in the subject.

11. The use according to any one of claims 1, 4 to 10, wherein the antibody or antigen-binding fragment thereof is formulated in a medicament for administration to the subject less than 4 hours after manifestation of one or more allergic symptoms in the subject.

12. The use according to any one of claims 1, 4 to 11, wherein the allergic symptoms are selected from the group consisting ofurticaria, angioedema, rhinitis, asthma, vomiting, respiratory compromise, swollen lips, swollen tongue, and reduced blood pressure.

13. The use of claim 1, wherein the allergic reaction is anaphylaxis.

14. The use according to any one of claims 1, 4 to 13, wherein the antibody or antigen-binding fragment thereof is formulated in a medicament for administration to the subject as part of a therapeutic dosing regimen comprising once a week, once every two weeks, once every three weeks, or once a month dosing.

15. The use according to any one of claims 1, 2, 4 to 14, wherein the antibody or antigen-binding fragment thereof is formulated in a medicament for administration to the subject in combination with a second therapeutic agent selected from the group consisting of steroids, antihistamines, decongestants, and anti-IgE agents.

16. The use according to any one of claims 2, 4 and 5, wherein the SIT regimen comprises an up-dosing phase followed by a maintenance phase.

17. The use according to any one of claims 2, 4, 5 and 16, wherein the SIT regimen is a rush SIT regimen.

18. The use according to any one of claims 1 to 17, wherein the antibody or antigen-binding fragment thereof is formulated in a medicament for administration to the subject in an amount from 0.5 mg to 600 mg.

19. The use according to claim 18, wherein the antibody or antigen-binding fragment thereof is formulated in a medicament for administration to the subject in an amount of 300 mg.

20. The use according to any one of claims 1 to 19, wherein the medicament is formulated to deliver the IL-4R antagonist subcutaneously.

21. The use according to any one of claims 1 to 20, wherein:
(a) the medicament is contained in a syringe; (b)the medicament is contained in a pen delivery device; or (c) the medicament is contained in a prefilled pen delivery device.