Published in final edited form as:

J Allergy Clin Immunol. 2015 February ; 135(2): 312–323. doi:10.1016/j.jaci.2014.12.1908.

The Future of Biologics: Applications for Food Allergy

Rebecca N. Bauer¹, Monali Manohar¹, Anne Marie Singh², David C. Jay¹, and Kari C. Nadeau^{*,1}

¹Division of Pediatric Immunology, Allergy, and Rheumatology, Department of Pediatrics, Stanford University School of Medicine, Stanford, CA

²Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, IL

Abstract

Allergic diseases affects millions worldwide, with growing evidence of an increase in allergy occurrence over the past few decades. Current treatments for allergy include corticosteroids to reduce inflammation and allergen immunotherapy (AIT); however, some individuals experience treatment-resistant inflammation or adverse reactions to these treatments, and neither are currently approved for the treatment of food allergy. There is a dire need for new therapeutic approaches for individuals with poorly controlled atopic diseases and to improve the safety and effectiveness of AIT. Improved understanding of allergy through animal models and clinical trials has unveiled potential targets for new therapies, leading to the development of several biologics to treat allergic diseases. This review focuses on the mechanisms that contribute to allergy, with an emphasis on future targets for biologics for the treatment of food allergy. These biologics include immunotherapy with novel anti-IgE antibodies and analogs, small molecule inhibitors of cell signaling, anti-type 2 cytokine monoclonal antibodies and Th1-promoting adjuvants.

Keywords

food allergy; immunotherapy; anti-IgE; oral tolerance; allergen sensitization; anaphylaxis; biologics

Introduction

Hundreds of millions of people worldwide are affected by atopic diseases, including atopic dermatitis, allergic rhinitis, food allergy and allergic asthma, and the frequency has continued to rise over the past several decades.^{1, 2} A clear progression from early life atopic dermatitis to later allergic rhinitis, food allergy, and asthma has been commonly observed,

*Address correspondence to: Kari Nadeau, MD, PhD, FAAAAI, 269 Campus Drive, CCSR Building, Room 3215, Stanford University, Stanford, CA 94305. Phone: 650-867-4592. Fax: 650-498-5560. knadeau@stanford.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

and is now termed “atopic march.”² Atopy links these diseases, manifesting as excessive production of IgE antibodies and hypersensitivity to environmental and food triggers.

Current standard therapies for atopic diseases involve treatment with corticosteroids to reduce inflammation, anti-histamines and leukotriene inhibitors, allergen immunotherapy (AIT), and allergen avoidance.^{3–6} Though these therapies control symptoms for the majority of patients, some individuals experience treatment-resistant inflammation or adverse reactions. Thus, there is a pressing need for new therapeutic approaches to treat individuals with poorly controlled atopic diseases.

Current research is focused on identifying new targets for the development of biologics, or biopharmaceuticals derived from natural sources like humans, animals or microorganisms, to treat atopic diseases.⁷ Most current biologic treatments are monoclonal antibodies directed against IgE and cytokines, such as IL-4 and IL-5 produced by Type 2 (Th2) T helper cells, eosinophils, mast cells, innate lymphoid (ILC) cells and basophils that promote allergic inflammation.⁸ Omalizumab, an IgE-targeted monoclonal antibody, is the only approved biologic for treatment of allergic disease, but presently only for use in patients with asthma or chronic urticaria.^{9, 10} Responses to cytokine-directed therapies have been variable, likely due to the heterogeneity of allergy and asthma phenotypes, but therapies targeting specific patient populations, such as anti-IL-4R α antibodies in patients with persistent Th2-driven asthma, have proven more successful.¹¹ Thus, there is interest in molecular phenotyping and developing biologics that may improve options for personalized medicine approaches to allergy.

The status of biological agents for the treatment of asthma and atopic dermatitis is reviewed elsewhere in this edition of the *Journal of Allergy and Clinical Immunology*. Here, we will review the general mechanisms that contribute to atopy with an emphasis on food allergy and discuss future targets for biologics to treat food allergy, a disease lacking any approved therapeutic options.

Food Allergy Overview

Food allergy is as an immune-mediated response to food proteins leading to symptoms affecting the skin, gastrointestinal (GI) tract or respiratory tract. Up to 8% of children and 5% of adults self-reported an allergy to at least one food.¹² Incidence of food allergy has steadily increased by over 18% between 1997 and 2007, suggesting that environmental influences may promote food allergy.¹³ The term food allergy encompasses both IgE and non-IgE-mediated diseases, including eosinophilic esophagitis and food protein-induced enterocolitis syndrome. This review will focus on IgE-mediated food allergies. Other recent reviews have covered non-IgE-mediated disorders.^{14, 15}

Despite the increasing prevalence of food allergy, there are currently no approved treatments beyond allergen avoidance and treatment of reactions to accidental ingestion. The reported rates of reaction to accidental ingestion vary widely, with some reports indicating 5% per year for peanut allergy and 42% per year for milk allergy.^{16, 17} Though incidence of food

allergy-related mortality is low, avoidance and fear of accidental ingestion significantly impairs quality of life for children with food allergy and their caregivers.¹⁸

Oral and sublingual AIT for the treatment of food allergy is an area of active investigation.^{19–21} AIT involves the gradual increase of exposure to food allergens to induce desensitization and promote permanent immunologic tolerance to the food allergen.²² While the efficacy of AIT for food allergy is still being actively investigated, the considerable rate of adverse reactions, the lengthy time required for therapy and evidence of rapidly waning protection upon cessation of active therapy for many patients, are already emerging as significant limitations.^{23, 24} Thus, there is a need for new alternatives or adjunctive therapies that improve the safety and effectiveness of AIT.

Recently, there has been increased interest in the use of biologics for the treatment of allergic diseases, particularly asthma. Relatively few studies have investigated applications of biologics for the treatment of food allergy. Below we will outline the pathophysiology of allergy in the context of food allergy and current or proposed targets for the development of future biologics.

Mechanisms of Allergy

Allergy is characterized by pronounced type 2 inflammatory responses and circulating and cell-bound allergen-specific IgE. The pathophysiology of allergy is thought to involve three main mechanisms: breakdown of tolerance; allergen sensitization; and allergen reactivity leading to anaphylaxis.

Tolerance

Tolerance is the mechanism by which potentially antigenic substances do not elicit an immune response.²⁵ Tolerance is mediated by several immune cells, including antigen presentation cells, such as dendritic cells (DCs) and macrophages, as well as regulatory T cells (Treg), which are important suppressors of cellular and humoral immune responses (Figure 1). DCs at mucosal surfaces sample luminal contents through the epithelium, receive antigens delivered by goblet cells, or internalize or acquire antigen at secondary lymphoid tissues.^{26–28} Following antigen recognition, DCs migrate to lymph nodes for antigen presentation to T cells, which is thought to be crucial for the development of tolerance. For example, CX CR1⁺CD103⁺ DCs in the gut home to the mesenteric lymph node where they induce the generation of CD4⁺Foxp3⁺ Tregs and IL-10-producing type 1 regulatory (Tr1) cells through the production of retinoic acid and TGF- β .^{29–31} Notably, a recent study has suggested that lymph node-resident DCs, and not migratory DCs, may have a more critical tolerogenic role following antigen exposure.^{32, 33}

Tregs are important mediators of tolerance and suppress immune responses via the production of immune-regulating cytokines, such as IL-10 and TGF β , and cell-mediated inhibition of naïve T cell proliferation and differentiation into effector and memory CD4⁺ and CD8⁺ T cells.^{34, 35} Tregs, together with suppressor CD8⁺ T cells, B cells, Tr1, Th3 and natural killer T (NKT) cells mediate oral tolerance after repeated low-dose exposure to antigens, whereas high-dose exposure to allergen promotes oral tolerance by inducing

lymphocyte anergy.^{36–40} Presently, studies indicate that Tregs and Tr1 cells, and their production of TGF- β and IL-10, may be important for tolerance induction during AIT for food allergy, but more in-depth studies and studies of other tolerogenic cell types are needed.⁴¹

Breakdown of Tolerance and Antigen Sensitization

Perturbation of tolerance promotes allergen sensitization, characterized by Th2-dominant immune responses and B cell class-switching toward IgE and IgG (Figure 2). Th2-driven inflammation is associated with increased levels of IL-4, IL-5 and IL-13.⁴² IL-4 induces Th2 proliferation, B cell isotype switching and mast cell development.^{43–45} IL-5 drives the growth, maturation, recruitment and activation of eosinophils.^{46, 47} IL-13 induces IgE synthesis, eosinophil and basophil recruitment, and epithelial cell mucus production and activity.^{48–51} Loss of oral tolerance is associated with diminished Treg responses, exemplified by patients with IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked), who have mutations in the FOXP3 locus and develop several severe allergic disorders.^{52, 53} Induction of Treg expansion and regulatory activity is associated with tolerance to allergens during successful immunotherapy.^{40, 41, 54–59}

The epithelium is also a key player in the development of allergy. Epithelial cells (ECs) at multiple sites, including the skin, lung, and gut, serve as a barrier against foreign proteins, and increased epithelial permeability is associated with antigen sensitization and allergy development.^{60, 61} ECs at multiple tissue sites produce cytokines and chemokines that promote Th2 skewing by DCs, including thymic stromal lymphopoietin (TSLP), IL-25, and IL-33. For example, in murine models of allergic asthma and food allergy, IL-33 production by IECs following sensitization promoted interactions between DCs and T cells, which augmented Th2 cell expansion and inhibition of Treg activity.⁶² TSLP, IL-25 and IL-33 from ECs also activates ILCs, which then also produce Th2 cytokines.^{63–65} These findings indicate the active contribution of epithelial cells to the development of allergic diseases.

Food allergy, specifically, is commonly associated with atopic dermatitis, implicating the skin as a possible route for food allergen sensitization.^{2, 66, 67} Mutations in the filaggrin gene, which encodes the epidermal filament-aggregating protein, is associated with decreased keratinocyte barrier function and an increased risk for development of food allergy.^{68–70} The skin is likely not the only way for allergen sensitization to occur for food allergy, as a recent study has found that lung DCs, similar to CD103⁺ DCs in the gut, can induce the migration of T cells to the GI tract following intranasal immunization.⁷¹ Thus, conceivably there could be other tissue sites for allergen sensitization to occur to food allergens, aside from the skin. These findings suggest that allergen sensitization and the development or perturbation of tolerance may be more nuanced in food allergy, varying by compartment and route of antigen exposure, making it unclear which routes and mechanisms are most important for the development of food allergy over other allergic diseases.

Reactivity to Allergen

Following allergen sensitization, re-exposure to allergens can cause anaphylaxis at both local and systemic sites.⁷² Anaphylaxis occurs in two phases following allergen exposure: an

acute reaction that occurs within minutes caused by cellular release of preformed mediators, and a late-phase response that occurs hours later and is mediated by the influx of inflammatory cells (Figure 3).⁷³

The acute phase response occurs when IgE antibodies bound by the high affinity receptor FcεRI expressed on mast cells and basophils recognizes allergens and then induces crosslinking and downstream activating signaling events.^{72, 74–76} Mast cells and basophils release a number of pre-formed mediators, including histamine, platelet-activating factor (PAF), and 5-hydroxytryptamine (5-HT).^{72, 77} Histamine and PAF induce vasodilation, vascular permeability, bronchoconstriction, increased heart rate, cardiac contraction, glandular secretion and leukocyte recruitment.^{77–79} Other pre-formed mast cell and basophil-derived mediators include proteases, lipid mediators and several cytokines.⁸⁰ Anaphylaxis mediated by IgG has also been described in the mouse, though it has not been demonstrated in humans.^{81, 82}

In some individuals, a late-phase anaphylactic reaction may occur after allergen exposure.^{77, 83} The late-phase reaction is induced by the secretion of mediators from immune cells recruited from the circulation, including eosinophils, basophils, and monocytes and T and B cells, as well as tissue-resident cells like mast cells and ECs.⁸³ These cells further produce inflammatory mediators and proteases that can damage tissue and induce anaphylactic symptoms.

Therapeutic implications for Food Allergy

Improved understanding of the cellular and molecular mechanisms that lead to altered immune tolerance and reactivity to food allergens may have important therapeutic implications. Blockage of IgE with omalizumab has been of much interest for the treatment of food allergy,⁸⁴ but alterations in Th1/Th2 cytokine balance, epithelial cell function, and other components of the IgE pathway also represent interesting targets. The current and potential therapeutics discussed below are listed in Table 1.

Modulating Th1/Th2 Imbalance

Anti-Cytokine Therapy

Th2-driven inflammatory responses are a key characteristic of allergic diseases like food allergy.⁴² Several studies have found increased levels of the Th2-associated cytokines IL-4, IL-5 and IL-13 in food allergic patients and mouse models of food allergy.^{85–89} Additionally, mutations in *IL-4 Receptor A (IL-4RA)* and *IL-13* are associated with increased risk of food allergy, highlighting the importance of Th2 cytokine signaling in food allergy.^{90, 91} Blockade of IL-4 and IL-13 signaling with the anti-IL-4Rα antibody dupilumab, successfully improved the clinical symptoms of subjects with asthma or atopic dermatitis, though other therapies blocking IL-4, IL-13 or IL-5 individually have been less effective.^{11, 92–94} Anti-cytokine therapies against a single cytokine seem to be less effective at managing clinical symptoms, possibly due to the redundant mechanisms of action of other Th2 cytokines. To date, no reported clinical trials have investigated the effectiveness of anti-Th2 cytokine treatments in context of IgE-mediated food allergy. However, in patients with

eosinophilic esophagitis (EoE), a non-IgE-mediated form of food allergy characterized by high levels of eosinophils in the esophagus after ingestion of a food allergen, treatment with the anti-IL-5 antibodies mepolizumab and reslizumab reduced eosinophilia, but had mixed effects on clinical symptoms.^{95–97} Studies of anti-cytokine therapies have been performed as monotherapies, and not in conjunction with AIT. Thus, using anti-cytokine treatment against multiple Th2 cytokines as an adjunctive therapy with AIT are needed to determine whether anti-cytokine treatment can help promote the clinical efficacy and/or safety of AIT.

TLR Agonist, Natural Polymer and Cell-Based Adjuvants

Another approach to altering Th1/Th2 imbalance is combining food allergen immunotherapy with Th1-promoting immune adjuvants.^{42, 98} Adjuvants can promote DC antigen internalization and Th1 polarization, restoring Th1/Th2 balance in Th2-driven allergic diseases. These adjuvants mimic pathogen-associated molecular patterns that bind to pattern recognition receptors, such as the Toll-like Receptors (TLRs) or C-type Lectin Receptors (CLRs). For example, in a mouse model of asthma, treatment with a TLR-7 agonist, R848, as a monotherapy, alleviated airway inflammation by targeting NKT cells, a source of Th2 cytokines during allergic inflammation, and promoted the Th1 cytokine production by NKT cells.⁹⁹ In contrast to anti-cytokine therapy studies, TLR agonists have been used as adjuvants in conjunction with AIT. Treatment with CpG oligodeoxynucleotides, which are recognized by TLR-9, coupled to a ragweed allergen, improved clinical symptoms in patients with allergic rhinitis.^{100, 101} Use of the TLR-4 agonist monophosphoryl lipid A (MPL), a LPS-derivative, as a Th1-promoting adjuvant in AIT successfully improved the clinical symptoms of allergic rhinoconjunctivitis in subjects undergoing short course immunotherapy for grass pollen and ragweed.^{102–104} Since TLR agonists strongly enhance Th1 responses, there is some concern whether TLR agonists may also diminish Treg induction during efficacious AIT.¹⁰⁵ However, there is some indication that Tregs induced during immunotherapy may actually work in concert with TLR agonists to suppress adverse Th2 responses.¹⁰⁶ This may have implications for more effective AIT for the treatment of food allergy. Long-term and detailed cellular studies of TLR agonists as adjuvants with AIT are needed to determine their effect on the development of tolerance.

Other Th1 adjuvants have also been proposed, including chitosan, a fungal cell wall component, and OMP-16, a membrane protein from *Brucella abortus*. Treatment of mice with peanut allergen bound to chitosan, or cow's milk protein bound to OMP-16, reduced allergen-specific IgE antibody responses and promoted Th1 responses.^{107, 108} These studies further suggest that promoting Th1 polarization may be an effective adjunctive therapy for the treatment of food allergy.

A final interesting alternative to AIT is to administer antigen-coupled splenocytes to alter Th1/Th2 imbalance and promote tolerance.¹⁰⁹ Antigen-coupled splenocytes have been shown to undergo apoptosis and are captured by host antigen presentation cells and presented to T cells in a tolerogenic manner.¹¹⁰ Treatment of mice with peanut extract-coupled splenocytes prior to peanut sensitization reduced Th2 responses and induced Tregs.¹⁰⁹ Clinical trials are underway to assess the safety and efficacy of these compounds for the induction of tolerance in the treatment of multiple sclerosis (EudraCT no.

2008-004408-29). Further, modulation of oral tolerance by cellular therapies that introduce patient-derived regulatory cells, such as Foxp3⁺ Tregs, into the host have been proposed for the treatment of allergic diseases by inhibiting adverse Th2 responses and promoting tolerance, though studies are needed to test the safety and efficacy of these treatments.⁵⁴

Epithelial Cell Targets

In addition to serving as a barrier, intestinal epithelial cells (IECs) actively contribute to the pathology of food allergy by interacting with allergens and secreting Th2-promoting mediators that influence DC activity.^{111–113} Though no specific epithelial cell therapeutics have been developed for the treatment of food allergy, we propose several candidates for future therapeutics.

IECs express CD23 (FcεRII), a low affinity IgE receptor that transports antigen-bound IgE across the epithelium to the underlying tissue.^{114, 115} Newly synthesized IgE is also transported back to the lumen by CD23 to be bound by allergens.¹¹⁶ Interestingly, CD23 expression by IECs is up-regulated by IL-4, and soluble CD23 is increased in stool samples from food allergic individuals, suggesting a role for CD23 in food allergy.^{116–118} In human cells, studies found that treatment with CD23 blocking antibodies prevents IgE transport by IECs.¹¹⁶ Though additional studies are necessary, the above findings suggest that CD23 is a promising target for inhibiting IgE transport by IECs in food allergy.

In response to allergens, the epithelium actively produces cytokines and chemokines, including TSLP and IL-33, which promote DC activation and Th2 polarization.^{112, 113, 119} Mutations in TSLP are associated with EoE, and mouse models suggest that TSLP is necessary for the development of EoE.^{120, 121} Interestingly, the function of TSLP may differ depending on anatomical location of the response. Epicutaneous sensitization to food allergen through skin lesions was shown to induce TSLP secretion by keratinocytes, which promoted basophil expansion and Th2 inflammation.¹²² In the gut, TSLP is constitutively secreted by IECs and contributes to both tissue homeostasis and promotion of Th2 responses.¹²³ Recently, TSLP was shown to be unnecessary for Th2-driven inflammation in the gut or oral sensitization to peanut allergen, in a mouse model of food allergy.⁶² These studies suggest that TSLP plays a complicated tissue-specific role in the development and progression food allergy. Whether blocking antibodies to TSLP would improve food allergy symptoms remains unclear, though early clinical trials for AMG 157, a monoclonal antibody directed against TSLP, showed a positive effect in reducing allergen-induced asthma responses and eosinophilia.¹²⁴

Contrary to findings for TSLP, IL-33 was shown to be necessary for sensitization to peanut allergens and allergic responses in mouse models of food allergy.^{62, 125} IL-33 promotes both mucosal permeability and Th2 skewing by DCs and ILCs.^{62, 126–128} Two studies using mouse models of allergic rhinitis or asthma have found that allergic inflammation can be attenuated by treatment with antibodies against IL-33, identifying IL-33 as a promising candidate for food allergy therapy.^{129, 130}

IgE pathway targets

IgE Production and Availability

Binding of food allergen to FcεRI-bound IgE on the surface of FcεRI-expressing immune cells, such as basophils and mast cells, induces crosslinking and triggers their activation and effector function, which can induce anaphylaxis. Thus, free and receptor-bound IgE antibodies represent therapeutic targets in the design of novel strategies to treat food allergy.¹³¹ Several clinical trials have successfully employed the anti-IgE monoclonal antibody, omalizumab, as an adjunctive therapy to food allergen AIT.^{40, 132–135} Omalizumab binds IgE, thereby preventing its binding to FcεRI and reducing serum levels of IgE by 99%.¹³⁶ By decreasing serum levels of IgE, omalizumab also indirectly reduces FcεRI expression on basophils, mast cells and dendritic cells, thereby diminishing degranulation and histamine release by basophils and mast cells, and allergen presentation by dendritic cells.^{137–141} Omalizumab is one of the most promising therapeutics for the treatment of food allergy, allowing the use of rapid dose escalation protocols for AIT in food allergic patients; though larger clinical trials are needed to assess overall efficacy and safety.^{132, 135} Omalizumab, however, binds IgE at the same site as FcεRI, and thus cannot directly interact with FcεRI-bound IgE, rendering omalizumab ineffective for disrupting IgE bound by FcεRI on the surface of immune cells.¹⁴² In addition, while omalizumab is approved for treatment of asthmatic subjects with serum IgE levels between 30 and 700 IU/ml, its efficacy in patients with asthma or atopic dermatitis with very high IgE levels (>700 IU/ml) is unclear.^{143, 144} Thus, other therapeutics targeting IgE production and availability are being developed.

Similar to omalizumab, QGE031 (ligelizumab) is a new anti-IgE antibody that binds free serum IgE, but with up to 12-times higher affinity, making it much more potent.¹⁴⁵ QGE031 was shown to be safe and to mediate greater suppression of free IgE and downregulation of FcεRI expression on basophils in treated atopic subjects compared to omalizumab.¹⁴⁵ Though omalizumab suppresses IgE on the order of 99%, FcεRI-expressing cells like basophils are remarkably sensitive to IgE-mediated stimulation.¹⁴⁶ Thus, having an anti-IgE therapeutic with a much higher binding affinity than omalizumab is attractive to further control IgE availability. This may greatly benefit patients with food allergies who are either unresponsive to or unable to be treated with omalizumab, particularly those subjects with very high serum IgE levels. Phase II trials are planned to assess the clinical efficacy of QGE031 in subjects with atopic dermatitis and asthma (NCT01552629; NCT01716754).

In addition to mediating IgE transport by IECs (described above), the low affinity IgE receptor CD23 (FcεRII) controls the synthesis, homeostasis and transport of IgE in B cells, making it a potential target to regulate serum IgE.¹⁴⁷ *In vitro* treatment of PBMCs with anti-CD23 reduced IgE production by B cells, proliferation of T cells, and production of IL-5, indicating that it may be a promising treatment for Th2-mediated allergic diseases.^{148, 149} Intranasal anti-CD23 treatment significantly decreased serum levels of allergen-specific IgE and IL-4 and partially inhibited Th2 responses in a mouse model of allergic rhinitis.¹⁵⁰ In a phase I trial, a single-dose of the anti-CD23 blocking antibody, lumiliximab, significantly reduced serum IgE levels in asthmatic patients, but had no effect on FEV1, a clinical marker

of asthma symptoms.¹⁵¹ However, this may be because of the heterogeneity of asthma in the study subjects. These findings indicate that anti-CD23 treatment may be an interesting substitute for omalizumab in food allergy therapy through its regulation of IgE production. However, it remains to be determined whether anti-CD23 treatment will also improve the clinical symptoms of food allergy, or be helpful as an adjunctive therapy in AIT.

In another novel approach, antibodies have been developed that bind to an extracellular sequence M1', which exists only on human membrane-bound IgE, and not free serum IgE.¹⁵² M1' is expressed exclusively by IgE-switched B cells, making it ideal for the specific targeting of IgE-expressing B cells. Upon crosslinking M1', apoptosis is induced in IgE-producing B cells, which then reduces serum IgE levels.^{153, 154} When the anti-M1' antibody, quilizumab, was tested in patients with moderate to severe allergic asthma, reductions in allergen-specific serum IgE and asthmatic responses were observed.¹⁵⁵ These findings indicate that deletion of IgE-producing B cells may also be effective for the treatment of food allergy. However, further studies are needed.

Inhibitory Receptors, IgE and FcεRI Disruption, and Signaling Blockade

Multiple human bispecific antibodies have been generated that crosslink and aggregate FcεRI with FcγRIIb, an inhibitory receptor specific for IgE. Binding to FcγRIIb suppresses downstream IgE signaling events, which has been shown to inhibit basophil and mast cell activation and degranulation.^{156, 157} Bispecific antibody approaches where the allergen is fused to the human IgGγ1 Fc region successfully inhibited degranulation of basophils from donors allergic to cat dander and blocked systemic and skin reactivity in a mouse model of cat dander allergic airway hypersensitivity.^{158, 159} Administration of another recombinant heterobivalent construct composed of the major peanut allergen Ara h 2 and human IgG Fcγ1 inhibited histamine release and anaphylaxis in a murine model of peanut allergy.¹⁶⁰ Thus, bispecific reagents may be effective substitutes to omalizumab as an adjunctive treatment, though it may be tedious and costly to make bispecific reagents for individual allergens, particularly when several epitopes may be recognized in an allergic individual.¹⁶¹ In addition, IgG antibodies induced following AIT have been shown to bind to FcγRIIb to suppress IgE-mediated hypersensitivity, implying that passive immunization with polyclonal food-specific IgG could be another alternative biologic in food allergy therapy.¹⁶²

Further, researchers have actively explored small molecule inhibitors and natural product analogs to target the FcεRI-IgE interaction.¹⁶³ Designed ankyrin repeat proteins (DARPs) are high-affinity inhibitors of IgE-FcεRI binding, as well as disruptors of preformed IgE-FcεRI complexes.¹⁶⁴ In a recent study, treatment with a novel DARPin (E2_79) rapidly disrupted IgE-FcεRI complexes on the surface of basophils and blocked IgE-dependent responses in a humanized mouse model of passive anaphylaxis.¹⁶⁵ In the same study, treatment with a bivalent DARPin (bi53_79), or two DARPins fused together, was more efficacious in reducing anaphylaxis than omalizumab. While studies of DARPins in the treatment of allergy are in their infancy, and future clinical trials are needed to test their safety and efficacy, these disruptive IgE inhibitors may be ideal therapeutics due to their potency and potential to reduce allergic symptoms.

Inhibitors of signaling molecules downstream of IgE-FcεRI may also represent interesting targets. In a mouse model of peanut allergy, blockade of spleen tyrosine kinase (syk), which is downstream of FcεRI, prevented peanut allergen sensitization and facilitated desensitization, partially through induction of Tregs.¹⁶⁶ Syk inhibition is not only a promising therapeutic, but highlights the importance of IgE signaling in the promotion of Th2 and regulatory responses in food allergy.

Mast Cell Anergy In an interesting twist to traditional oral allergen immunotherapy, administration of increasing doses of anti-IgE or anti-FcεRIα monoclonal antibody has been proposed. In mouse models of antigen and anti-IgE-induced anaphylaxis, mice are injected with a single large dose of anti-IgE or anti-FcεRIα that induces anaphylaxis.¹⁶⁷ However, when escalating doses of anti-IgE or anti-FcεRIα were administered, rapid desensitization was induced that prevented anaphylaxis.¹⁶⁸ Rapid desensitization with anti-FcεRIα was found to promote mast cell anergy and also to quickly remove FcεRI-bound IgE from mast cells, thus preventing any adverse effects mediated by IgE already bound by FcεRIα before the rapid desensitization protocol was begun. However, this induced mast cell anergy was short-lived. Clever bioengineering of anti-FcεRIα antibodies that prolong mast cell anergy may make this an interesting adjunctive approach for rapid desensitization of allergic subjects undergoing oral immunotherapy.

Conclusion

Despite the increasing prevalence of food allergy and adverse impact on human health and quality of life, there is an unmet need for effective therapeutic options to treat food allergy. Biologics represent a new avenue for the development of therapies that inhibit specific mechanisms of food allergy and, perhaps, prevent sensitization to food allergen in the first place. However, most studies of biologics for the treatment of allergic diseases have focused on asthma, allergic rhinitis, and atopic dermatitis, and future studies are necessary to test the efficacy of these therapeutics in food allergic patients. Current biologics inhibiting Th2 cytokines and free IgE through treatment with monoclonal antibodies and have had mixed success in allergic patients. Recent basic and clinical studies have identified attractive new targets for food allergy therapeutics, including epithelial cell-derived mediators (such as IL-33 and TSLP), IgE-binding receptors (such as CD23), and IgE signaling pathways. Continued advancement in the mechanistic understanding of food allergy gives hope that effective treatments will soon be available for this difficult to treat disease.

Abbreviations

(AIT)	allergen immunotherapy
(Th2)	type 2 helper
(DC)	dendritic cell
(Treg)	regulatory T cell
(Tr1)	type 1 regulatory cell

(NKT)	natural killer T cell
(IEC)	intestinal epithelial cell
(ILC)	innate lymphoid cell
(TSLP)	thymic stromal lymphopoietin
(PAF)	platelet activating factor
(5-HT)	5-hydroxytryptamine
(TLR)	toll-like receptor
(CLR)	C-type lectin receptor
(DARPin)	designed ankyrin repeat protein
(syk)	spleen tyrosine kinase
(EoE)	eosinophilic esophagitis

JACI-D-14-01376 Glossary

Antigen presentation cells (APCs)

cells that present foreign antigens via major histocompatibility complexes (MHCs) on their surfaces to T-cells via T-cell receptors (TCRs)

Th3 cells (T helper 3 cells)

T-cells that protect mucosal surfaces in the gut from nonpathogenic non-self antigens by secreting the anti-inflammatory cytokines TGF-beta and IL-10. Th3 cells inhibit Th1 and Th2 cells.

B cell class-switching

a mechanism that changes the antibody production of B cells to a different isotype

Thymic stromal lymphopoietin (TSLP)

A cytokine linked to allergic disease that stimulates the maturation of T cells through the activation of antigen presenting cells (APCs) such as dendritic cells and macrophages.

IL-25

a cytokine known to be involved in gut immunity that induces the type 2 cytokines: IL-4, IL-5 and IL-13

IL-33

from the IL-1 family of cytokines, IL-33 potently drives production of type 2 cytokines. It is also a ligand for IL33R (IL1RL1), an IL-1 family receptor that is selectively expressed on Th2 cells and mast cells.

OX40-OX40L

members of the tumor necrosis factor superfamily expressed on a variety of cells including activated CD4(+) and CD8(+) T cells. The OX40-OX40L complex has been shown to regulate cytokine production from T cells, antigen-presenting cells, natural killer cells, and natural killer T cells, and modulate cytokine receptor signaling. This complex plays a central role in the development of multiple inflammatory and autoimmune diseases, making them ideal therapeutic candidates.

FcεRI

the high-affinity receptor for the Fc region of immunoglobulin E (IgE), an antibody isotype involved in the allergic diseases and parasitic immunity

FcεRII (CD23)

the low-affinity receptor for IgE and involved in the regulation of IgE levels. Unlike many of the antibody receptors, CD23 is a C-type lectin found on mature B cells, activated macrophages, eosinophils, follicular dendritic cells, and platelets.

C-type lectin receptors (CLRs)

a large family of receptors that bind to carbohydrates in a calcium-dependent manner. These receptors are expressed on most cell types including macrophages and dendritic cells (DCs) and are involved in fungal recognition and the modulation of the innate immune response.

Platelet-activating factor (PAF)

A potent mediator of inflammatory responses that is a regulator of anaphylaxis. Studies have indicated that blocking the effects of PAF prevent fatal anaphylaxis.

IL-4 Receptor A (IL-4RA)

a protein that can bind IL-4 and IL-13 to regulate IgE antibody production in B cells and promote differentiation of Th2 cells

Toll-like receptors (TLRs)

a class of receptors expressed on macrophages and dendritic cells that recognize conserved microbial particles that can activate an immune response

CpG oligodeoxynucleotides

short single-stranded synthetic DNA molecules motifs that act as immunostimulants when unmethylated. CpG motifs are considered pathogen-associated molecular patterns (PAMPs) recognized by the pattern recognition receptor (PRR) Toll-Like Receptor 9 (TLR9), which is constitutively expressed only in B cells and plasmacytoid dendritic cells (pDCs).

Anergy

A state of immune unresponsiveness induced when a T cell receptor (TCR) is stimulated without a second signal from an antigen-presenting cell (APC)

PBMC (peripheral blood mononuclear cell)

blood cells consisting of lymphocytes (T cells, B cells, and NK cells), monocytes, and dendritic cells that characterized by a round nucleus

Spleen tyrosine kinase (syk)

an enzyme expressed in a variety of tissues that can transmit signals from the B-Cell receptor and T-Cell receptor as well as variety of other cell surface receptors

Metagenomics

a technology based on the genomic analysis of microbial DNA that is extracted directly from communities in environmental samples that enables a survey of the different microorganisms present in a specific environment. Metagenomics has the potential to unlock microbial diversity present in the environment to provide new molecules for therapeutic and biotechnological applications.

Comparative genomics

a field of biological research in which the genomic features of different organisms are compared, such as DNA sequence, genes, gene order, regulatory sequences, and other genomic structural landmarks

References

1. Pawankar, R.; Holgate, ST.; Canonica, GW.; Lockey, RF.; Blaiss, MS. The WAO White Book on Allergy. World Allergy Organization, Update; 2013.
2. Zheng T, Yu J, Oh MH, Zhu Z. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. *Allergy Asthma Immunol Res.* 2011; 3:67–73. [PubMed: 21461244]
3. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol.* 2010; 126:S1–58. [PubMed: 21134576]
4. Small P, Kim H. Allergic rhinitis. *Allergy Asthma Clin Immunol.* 2011; 7(Suppl 1):S3. [PubMed: 22166009]
5. Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, et al. Guidelines of care for the management of atopic dermatitis. *Journal of the American Academy of Dermatology.* 2014; 70:338–51. [PubMed: 24290431]
6. Expert Panel Report 3 (EPR-3). Guidelines for the Diagnosis and Management of Asthma—Summary Report 2007. *Journal of Allergy and Clinical Immunology.* 120:S94–S138. [PubMed: 17983880]
7. Rader RA. (Re)defining biopharmaceutical. *Nat Biotech.* 2008; 26:743–51.
8. Pelaia G, Vatrella A, Maselli R. The potential of biologics for the treatment of asthma. *Nat Rev Drug Discov.* 2012; 11:958–72. [PubMed: 23197041]
9. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, et al. Randomized Trial of Omalizumab (Anti-IgE) for Asthma in Inner-City Children. *New England Journal of Medicine.* 2011; 364:1005–15. [PubMed: 21410369]
10. Maurer M, Rosén K, Hsieh H-J, Saini S, Grattan C, Giménez-Arnau A, et al. Omalizumab for the Treatment of Chronic Idiopathic or Spontaneous Urticaria. *New England Journal of Medicine.* 2013; 368:924–35. [PubMed: 23432142]
11. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al. Dupilumab in Persistent Asthma with Elevated Eosinophil Levels. *New England Journal of Medicine.* 2013; 368:2455–66. [PubMed: 23688323]
12. Sicherer SH, Sampson HA. Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment. *Journal of Allergy and Clinical Immunology.* 133:291–307.e5.
13. Branum AM, Lukacs SL. Food allergy among children in the United States. *Pediatrics.* 2009; 124:1549–55. [PubMed: 19917585]
14. Kern E, Hirano I. Emerging drugs for eosinophilic esophagitis. *Expert Opin Emerg Drugs.* 2013; 18:353–64. [PubMed: 23937314]

15. Jarvinen KM, Nowak-Wegrzyn A. Food protein-induced enterocolitis syndrome (FPIES): current management strategies and review of the literature. *J Allergy Clin Immunol Pract.* 2013; 1:317–22. [PubMed: 24565536]
16. Neuman-Sunshine DL, Eckman JA, Keet CA, Matsui EC, Peng RD, Lenehan PJ, et al. The natural history of persistent peanut allergy. *Ann Allergy Asthma Immunol.* 2012; 108:326–31.e3. [PubMed: 22541403]
17. Fleischer DM, Perry TT, Atkins D, Wood RA, Burks AW, Jones SM, et al. Allergic reactions to foods in preschool-aged children in a prospective observational food allergy study. *Pediatrics.* 2012; 130:e25–32. [PubMed: 22732173]
18. Otani I, Begin P, Kearney C, Dominguez T, Mehrotra A, Bacal L, et al. Multiple-allergen oral immunotherapy improves quality of life in caregivers of food-allergic pediatric subjects. *Allergy, Asthma & Clinical Immunology.* 2014; 10:25.
19. Cavkaytar O, Akdis CA, Akdis M. Modulation of immune responses by immunotherapy in allergic diseases. *Curr Opin Pharmacol.* 2014; 17c:30–7.
20. Anagnostou K, Islam S, King Y, Foley L, Pasea L, Bond S, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. *The Lancet.* 383:1297–304.
21. Suárez-Fueyo A, Ramos T, Galán A, Jimeno L, Wurtzen PA, Marin A, et al. Grass tablet sublingual immunotherapy downregulates the TH2 cytokine response followed by regulatory T-cell generation. *Journal of Allergy and Clinical Immunology.* 2014; 133:130–8.e2. [PubMed: 24290282]
22. Vickery BP, Scurlock AM, Kulis M, Steele PH, Kamilaris J, Berglund JP, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. *Journal of Allergy and Clinical Immunology.* 2014; 133:468–75.e6. [PubMed: 24361082]
23. Sampson HA. Peanut oral immunotherapy: is it ready for clinical practice? *J Allergy Clin Immunol Pract.* 2013; 1:15–21. [PubMed: 24229817]
24. Lin SY, Erekosima N, Kim JM, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: A systematic review. *JAMA.* 2013; 309:1278–88. [PubMed: 23532243]
25. Wang J, Sampson HA. Food allergy. *J Clin Invest.* 2011; 121:827–35. [PubMed: 21364287]
26. McDole JR, Wheeler LW, McDonald KG, Wang B, Konjufca V, Knoop KA, et al. Goblet cells deliver luminal antigen to CD103+ dendritic cells in the small intestine. *Nature.* 2012; 483:345–9. [PubMed: 22422267]
27. Rescigno M, Urbano M, Valzasina B, Francolini M, Rotta G, Bonasio R, et al. Dendritic cells express tight junction proteins and penetrate gut epithelial monolayers to sample bacteria. *Nat Immunol.* 2001; 2:361–7. [PubMed: 11276208]
28. Lelouard H, Fallet M, de Bovis B, Meresse S, Gorvel JP. Peyer's patch dendritic cells sample antigens by extending dendrites through M cell-specific transcellular pores. *Gastroenterology.* 2012; 142:592–601.e3. [PubMed: 22155637]
29. Coombes JL, Siddiqui KR, Arancibia-Carcamo CV, Hall J, Sun CM, Belkaid Y, et al. A functionally specialized population of mucosal CD103+ DCs induces Foxp3+ regulatory T cells via a TGF-beta and retinoic acid-dependent mechanism. *J Exp Med.* 2007; 204:1757–64. [PubMed: 17620361]
30. Bakdash G, Vogelpoel LT, van Capel TM, Kapsenberg ML, de Jong EC. Retinoic acid primes human dendritic cells to induce gut-homing, IL-10-producing regulatory T cells. *Mucosal Immunol.* 2014
31. Sun C-M, Hall JA, Blank RB, Bouladoux N, Oukka M, Mora JR, et al. Small intestine lamina propria dendritic cells promote de novo generation of Foxp3 T reg cells via retinoic acid. *The Journal of Experimental Medicine.* 2007; 204:1775–85. [PubMed: 17620362]
32. Spahn TW, Weiner HL, Rennert PD, Luger N, Fontana A, Domschke W, et al. Mesenteric lymph nodes are critical for the induction of high-dose oral tolerance in the absence of Peyer's patches. *Eur J Immunol.* 2002; 32:1109–13. [PubMed: 11920578]

33. Anandasabapathy N, Feder R, Mollah S, Tse S-W, Longhi MP, Mehendru S, et al. Classical Flt3L-dependent dendritic cells control immunity to protein vaccine. *The Journal of Experimental Medicine*. 2014; 211:1875–91. [PubMed: 25135299]
34. Marie JC, Letterio JJ, Gavin M, Rudensky AY. TGF- β 1 maintains suppressor function and Foxp3 expression in CD4+CD25+ regulatory T cells. *The Journal of Experimental Medicine*. 2005; 201:1061–7. [PubMed: 15809351]
35. Rubtsov YP, Rasmussen JP, Chi EY, Fontenot J, Castelli L, Ye X, et al. Regulatory T Cell-Derived Interleukin-10 Limits Inflammation at Environmental Interfaces. *Immunity*. 2008; 28:546–58. [PubMed: 18387831]
36. Barone KS, Jain SL, Michael JG. Effect of in vivo depletion of CD4+ and CD8+ cells on the induction and maintenance of oral tolerance. *Cell Immunol*. 1995; 163:19–29. [PubMed: 7758127]
37. Kim HJ, Hwang SJ, Kim BK, Jung KC, Chung DH. NKT cells play critical roles in the induction of oral tolerance by inducing regulatory T cells producing IL-10 and transforming growth factor beta, and by clonally deleting antigen-specific T cells. *Immunology*. 2006; 118:101–11. [PubMed: 16630027]
38. Liu ZQ, Wu Y, Song JP, Liu X, Liu Z, Zheng PY, et al. Tolerogenic CX3CR1+ B cells suppress food allergy-induced intestinal inflammation in mice. *Allergy*. 2013; 68:1241–8. [PubMed: 24033604]
39. Friedman A, Weiner HL. Induction of anergy or active suppression following oral tolerance is determined by antigen dosage. *Proc Natl Acad Sci U S A*. 1994; 91:6688–92. [PubMed: 8022835]
40. Bedoret D, Singh AK, Shaw V, Hoyte EG, Hamilton R, DeKruyff RH, et al. Changes in antigen-specific T-cell number and function during oral desensitization in cow's milk allergy enabled with omalizumab. *Mucosal Immunol*. 2012; 5:267–76. [PubMed: 22318492]
41. Syed A, Garcia MA, Lyu S-C, Bucayu R, Kohli A, Ishida S, et al. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). *Journal of Allergy and Clinical Immunology*. 2014; 133:500–10.e11. [PubMed: 24636474]
42. Berin MC, Shreffler WG. T(H)2 adjuvants: implications for food allergy. *J Allergy Clin Immunol*. 2008; 121:1311–20. quiz 21–2. [PubMed: 18539190]
43. Bischoff SC, Sellge G, Lorentz A, Sebald W, Raab R, Manns MP. IL-4 enhances proliferation and mediator release in mature human mast cells. *Proceedings of the National Academy of Sciences*. 1999; 96:8080–5.
44. Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *The Journal of Immunology*. 1986; 136:2348–57. [PubMed: 2419430]
45. Finkelman FD, Katona IM, Urban JF, Holmes J, Ohara J, Tung AS, et al. IL-4 is required to generate and sustain in vivo IgE responses. *The Journal of Immunology*. 1988; 141:2335–41. [PubMed: 2459206]
46. Sur S, Kita H, Gleich GJ, Chenier TC, Hunt LW. Eosinophil recruitment is associated with IL-5, but not with RANTES, twenty-four hours after allergen challenge. *Journal of Allergy and Clinical Immunology*. 1997; 99:1272–8.
47. Yamaguchi Y, Suda T, Suda J, Eguchi M, Miura Y, Harada N, et al. Purified interleukin 5 supports the terminal differentiation and proliferation of murine eosinophilic precursors. *The Journal of Experimental Medicine*. 1988; 167:43–56. [PubMed: 3257253]
48. Punnonen J, de Vries JE. IL-13 induces proliferation, Ig isotype switching, and Ig synthesis by immature human fetal B cells. *The Journal of Immunology*. 1994; 152:1094–102. [PubMed: 7507958]
49. Pope SM, Brandt EB, Mishra A, Hogan SP, Zimmermann N, Matthaei KI, et al. IL-13 induces eosinophil recruitment into the lung by an IL-5- and eotaxin-dependent mechanism. *Journal of Allergy and Clinical Immunology*. 2003; 111:594–601.
50. Voehringer D, Reese TA, Huang X, Shinkai K, Locksley RM. Type 2 immunity is controlled by IL-4/IL-13 expression in hematopoietic non-eosinophil cells of the innate immune system. *The Journal of Experimental Medicine*. 2006; 203:1435–46. [PubMed: 16702603]

51. Kuperman DA, Huang X, Koth LL, Chang GH, Dolganov GM, Zhu Z, et al. Direct effects of interleukin-13 on epithelial cells cause airway hyperreactivity and mucus overproduction in asthma. *Nat Med*. 2002; 8:885–9. [PubMed: 12091879]
52. Bennett CL, Christie J, Ramsdell F, Brunkow ME, Ferguson PJ, Whitesell L, et al. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. *Nat Genet*. 2001; 27:20–1. [PubMed: 11137993]
53. Torgerson TR, Linane A, Moes N, Anover S, Mateo V, Rieux-Laucat F, et al. Severe food allergy as a variant of IPEX syndrome caused by a deletion in a noncoding region of the FOXP3 gene. *Gastroenterology*. 2007; 132:1705–17. [PubMed: 17484868]
54. Miyara M, Wing K, Sakaguchi S. Therapeutic approaches to allergy and autoimmunity based on FoxP3+ regulatory T-cell activation and expansion. *Journal of Allergy and Clinical Immunology*. 2009; 123:749–55. [PubMed: 19348913]
55. Oyoshi MK, Oettgen HC, Chatila TA, Geha RS, Bryce PJ. Food allergy: Insights into etiology, prevention, and treatment provided by murine models. *Journal of Allergy and Clinical Immunology*. 2014; 133:309–17. [PubMed: 24636470]
56. Savilahti EM, Savilahti E. Development of natural tolerance and induced desensitization in cow's milk allergy. *Pediatric Allergy and Immunology*. 2013; 24:114–21. [PubMed: 22957704]
57. Shreffler WG, Wanich N, Moloney M, Nowak-Wegrzyn A, Sampson HA. Association of allergen-specific regulatory T cells with the onset of clinical tolerance to milk protein. *Journal of Allergy and Clinical Immunology*. 2009; 123:43–52.e7. [PubMed: 19130927]
58. Swamy RS, Reshamwala N, Hunter T, Vissamsetti S, Santos CB, Baroody FM, et al. Epigenetic modifications and improved regulatory T-cell function in subjects undergoing dual sublingual immunotherapy. *Journal of Allergy and Clinical Immunology*. 2012; 130:215–24.e7. [PubMed: 22677046]
59. Scadding GW, Shamji MH, Jacobson MR, Lee DI, Wilson D, Lima MT, et al. Sublingual grass pollen immunotherapy is associated with increases in sublingual Foxp3-expressing cells and elevated allergen-specific immunoglobulin G4, immunoglobulin A and serum inhibitory activity for immunoglobulin E-facilitated allergen binding to B cells. *Clinical & Experimental Allergy*. 2010; 40:598–606. [PubMed: 20184605]
60. Turner JR. Intestinal mucosal barrier function in health and disease. *Nat Rev Immunol*. 2009; 9:799–809. [PubMed: 19855405]
61. Ventura MT, Polimeno L, Amoroso AC, Gatti F, Annoscia E, Marinaro M, et al. Intestinal permeability in patients with adverse reactions to food. *Dig Liver Dis*. 2006; 38:732–6. [PubMed: 16880015]
62. Chu DK, Llop-Guevara A, Walker TD, Flader K, Goncharova S, Boudreau JE, et al. IL-33, but not thymic stromal lymphopoietin or IL-25, is central to mite and peanut allergic sensitization. *J Allergy Clin Immunol*. 2013; 131:187–200.e1-8. [PubMed: 23006545]
63. Saenz SA, Siracusa MC, Monticelli LA, Ziegler CGK, Kim BS, Brestoff JR, et al. IL-25 simultaneously elicits distinct populations of innate lymphoid cells and multipotent progenitor type 2 (MP2) cells. *The Journal of Experimental Medicine*. 2013; 210:1823–37. [PubMed: 23960191]
64. Leyva-Castillo JM, Hener P, Michea P, Karasuyama H, Chan S, Soumelis V, et al. Skin thymic stromal lymphopoietin initiates Th2 responses through an orchestrated immune cascade. *Nat Commun*. 2013; 4
65. Kim HY, Chang Y-J, Subramanian S, Lee H-H, Albacker LA, Matangkasombut P, et al. Innate lymphoid cells responding to IL-33 mediate airway hyperreactivity independently of adaptive immunity. *Journal of Allergy and Clinical Immunology*. 2012; 129:216–27.e6. [PubMed: 22119406]
66. Reekers R, Busche M, Wittmann M, Kapp A, Werfel T. Birch pollen-related foods trigger atopic dermatitis in patients with specific cutaneous T-cell responses to birch pollen antigens. *Journal of Allergy and Clinical Immunology*. 1999; 104:466–72. [PubMed: 10452773]
67. Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BA, Sampson HA. Prevalence of IgE-Mediated Food Allergy Among Children With Atopic Dermatitis. *Pediatrics*. 1998; 101:e8.

68. Venkataraman D, Soto-Ramirez N, Kurukulaaratchy RJ, Holloway JW, Karmaus W, Ewart SL, et al. Filaggrin loss-of-function mutations are associated with food allergy in childhood and adolescence. *J Allergy Clin Immunol*. 2014
69. Brough HA, Simpson A, Makinson K, Hankinson J, Brown S, Douiri A, et al. Peanut allergy: Effect of environmental peanut exposure in children with filaggrin loss-of-function mutations. *Journal of Allergy and Clinical Immunology*. 2014; 134:867–75.e1. [PubMed: 25282568]
70. Asai Y, Greenwood C, Hull PR, Alizadehfard R, Ben-Shoshan M, Brown SJ, et al. Filaggrin gene mutation associations with peanut allergy persist despite variations in peanut allergy diagnostic criteria or asthma status. *Journal of Allergy and Clinical Immunology*. 2013; 132:239–42.e7. [PubMed: 23684069]
71. Ruane D, Brane L, Reis BS, Cheong C, Poles J, Do Y, et al. Lung dendritic cells induce migration of protective T cells to the gastrointestinal tract. *The Journal of Experimental Medicine*. 2013; 210:1871–88. [PubMed: 23960190]
72. Peavy RD, Metcalfe DD. Understanding the mechanisms of anaphylaxis. *Curr Opin Allergy Clin Immunol*. 2008; 8:310–5. [PubMed: 18596587]
73. Lieberman P. Biphasic anaphylactic reactions. *Ann Allergy Asthma Immunol*. 2005; 95:217–26. quiz 26, 58. [PubMed: 16200811]
74. Kraft S, Kinet JP. New developments in FcεRI regulation, function and inhibition. *Nat Rev Immunol*. 2007; 7:365–78. [PubMed: 17438574]
75. Wang M, Takeda K, Shiraishi Y, Okamoto M, Dakhama A, Joetham A, et al. Peanut-induced intestinal allergy is mediated through a mast cell–IgE–FcεRI–IL-13 pathway. *Journal of Allergy and Clinical Immunology*. 2010; 126:306–16.e12. [PubMed: 20624645]
76. Sihra BS, Kon OM, Grant JA, Kay AB. Expression of high-affinity IgE receptors (FcεRI) on peripheral blood basophils, monocytes, and eosinophils in atopic and nonatopic subjects: Relationship to total serum IgE concentrations. *Journal of Allergy and Clinical Immunology*. 99:699–706.
77. Brown SG, Stone SF, Fatovich DM, Burrows SA, Holdgate A, Celenza A, et al. Anaphylaxis: clinical patterns, mediator release, and severity. *J Allergy Clin Immunol*. 2013; 132:1141–9.e5. [PubMed: 23915715]
78. Vadas P, Gold M, Perelman B, Liss GM, Lack G, Blyth T, et al. Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. *N Engl J Med*. 2008; 358:28–35. [PubMed: 18172172]
79. Vadas P, Perelman B, Liss G. Platelet-activating factor, histamine, and tryptase levels in human anaphylaxis. *Journal of Allergy and Clinical Immunology*. 131:144–9.
80. Kurashima Y, Kiyono H. New era for mucosal mast cells: their roles in inflammation, allergic immune responses and adjuvant development. *Exp Mol Med*. 2014; 46:e83. [PubMed: 24626169]
81. Arias K, Chu DK, Flader K, Botelho F, Walker T, Arias N, et al. Distinct immune effector pathways contribute to the full expression of peanut-induced anaphylactic reactions in mice. *J Allergy Clin Immunol*. 2011; 127:1552–61.e1. [PubMed: 21624619]
82. Miyajima I, Dombrowicz D, Martin TR, Ravetch JV, Kinet JP, Galli SJ. Systemic anaphylaxis in the mouse can be mediated largely through IgG1 and Fc gammaRIII. Assessment of the cardiopulmonary changes, mast cell degranulation, and death associated with active or IgE- or IgG1-dependent passive anaphylaxis. *J Clin Invest*. 1997; 99:901–14. [PubMed: 9062348]
83. Galli SJ, Tsai M, Piliponsky AM. The development of allergic inflammation. *Nature*. 2008; 454:445–54. [PubMed: 18650915]
84. Syed A, Kohli A, Nadeau KC. Food allergy diagnosis and therapy: where are we now? *Immunotherapy*. 2013; 5:931–44. [PubMed: 23998729]
85. Prescott VE, Forbes E, Foster PS, Matthaei K, Hogan SP. Mechanistic analysis of experimental food allergen-induced cutaneous reactions. *J Leukoc Biol*. 2006; 80:258–66. [PubMed: 16861616]
86. Cardoso CR, Provinciatto PR, Godoi DF, Ferreira BR, Teixeira G, Rossi MA, et al. IL-4 regulates susceptibility to intestinal inflammation in murine food allergy. *Am J Physiol Gastrointest Liver Physiol*. 2009; 296:G593–600. [PubMed: 19136382]
87. Michaud B, Aroulandom J, Baiz N, Amat F, Gouvis-Echraghi R, Candon S, et al. Casein-specific IL-4- and IL-13-secreting T cells: a tool to implement diagnosis of cow's milk allergy. *Allergy*. 2014

88. Sicherer SH, Wood RA, Stablein D, Burks AW, Liu AH, Jones SM, et al. Immunologic features of infants with milk or egg allergy enrolled in an observational study (Consortium of Food Allergy Research) of food allergy. *J Allergy Clin Immunol.* 2010; 125:1077–83.e8. [PubMed: 20451041]
89. Kim EH, Bird JA, Kulis M, Laubach S, Pons L, Shreffler W, et al. Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. *J Allergy Clin Immunol.* 2011; 127:640–6.e1. [PubMed: 21281959]
90. Zitnik SE, Ruschendorf F, Muller S, Sengler C, Lee YA, Griffioen RW, et al. IL13 variants are associated with total serum IgE and early sensitization to food allergens in children with atopic dermatitis. *Pediatr Allergy Immunol.* 2009; 20:551–5. [PubMed: 19220774]
91. Liu X, Beatty TH, Deindl P, Huang SK, Lau S, Sommerfeld C, et al. Associations between specific serum IgE response and 6 variants within the genes IL4, IL13, and IL4RA in German children: the German Multicenter Atopy Study. *J Allergy Clin Immunol.* 2004; 113:489–95. [PubMed: 15007352]
92. Wenzel S, Wilbraham D, Fuller R, Getz EB, Longphre M. Effect of an interleukin-4 variant on late phase asthmatic response to allergen challenge in asthmatic patients: results of two phase 2a studies. *The Lancet.* 2007; 370:1422–31.
93. Corren J, Busse W, Meltzer EO, Mansfield L, Bensch G, Fahrenholz J, et al. A Randomized, Controlled, Phase 2 Study of AMG 317, an IL-4Ra Antagonist, in Patients with Asthma. *American Journal of Respiratory and Critical Care Medicine.* 2010; 181:788–96. [PubMed: 20056900]
94. Beck LA, Thaçi D, Hamilton JD, Graham NM, Bieber T, Rocklin R, et al. Dupilumab Treatment in Adults with Moderate-to-Severe Atopic Dermatitis. *New England Journal of Medicine.* 2014; 371:130–9. [PubMed: 25006719]
95. Straumann A, Conus S, Grzonka P, Kita H, Kephart G, Bussmann C, et al. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. *Gut.* 2010; 59:21–30. [PubMed: 19828470]
96. Stein ML, Collins MH, Villanueva JM, Kushner JP, Putnam PE, Buckmeier BK, et al. Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis. *J Allergy Clin Immunol.* 2006; 118:1312–9. [PubMed: 17157662]
97. Spergel JM, Rothenberg ME, Collins MH, Furuta GT, Markowitz JE, Fuchs G 3rd, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol.* 2012; 129:456–63. 63.e1–3. [PubMed: 22206777]
98. Keet CA, Wood RA. Emerging therapies for food allergy. *J Clin Invest.* 2014; 124:1880–6. [PubMed: 24789880]
99. Grela F, Aumeunier A, Bardel E, Van LP, Bourgeois E, Vanoirbeek J, et al. The TLR7 Agonist R848 Alleviates Allergic Inflammation by Targeting Invariant NKT Cells To Produce IFN- γ . *The Journal of Immunology.* 2011; 186:284–90. [PubMed: 21131420]
100. Creticos PS, Schroeder JT, Hamilton RG, Balcer-Whaley SL, Khattignavong AP, Lindblad R, et al. Immunotherapy with a ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis. *N Engl J Med.* 2006; 355:1445–55. [PubMed: 17021320]
101. Tulic MK, Fiset PO, Christodouloupoulos P, Vaillancourt P, Desrosiers M, Lavigne F, et al. Amb a 1-immunostimulatory oligodeoxynucleotide conjugate immunotherapy decreases the nasal inflammatory response. *J Allergy Clin Immunol.* 2004; 113:235–41. [PubMed: 14767435]
102. Rosewich M, Schulze J, Eickmeier O, Telles T, Rose MA, Schubert R, et al. Tolerance induction after specific immunotherapy with pollen allergoids adjuvanted by monophosphoryl lipid A in children. *Clinical & Experimental Immunology.* 2010; 160:403–10. [PubMed: 20345983]
103. Patel P, Holdich T, Fischer von Weikersthal-Drachenberg KJ, Huber B. Efficacy of a short course of specific immunotherapy in patients with allergic rhinoconjunctivitis to ragweed pollen. *Journal of Allergy and Clinical Immunology.* 2014; 133:121–9.e2. [PubMed: 23870670]
104. DuBuske LM, Frew AJ, Horak F, Keith PK, Corrigan CJ, Aberer W, et al. Ultrashort-specific immunotherapy successfully treats seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy and Asthma Proceedings.* 2011; 32:239–47. [PubMed: 21535913]

105. Mittag D, Varese N, Scholzen A, Mansell A, Barker G, Rice G, et al. TLR ligands of ryegrass pollen microbial contaminants enhance Th1 and Th2 responses and decrease induction of Foxp3hi regulatory T cells. *European Journal of Immunology*. 2013; 43:723–33. [PubMed: 23238878]
106. Tsai Y-G, Yang KD, Niu D-M, Chien J-W, Lin C-Y. TLR2 Agonists Enhance CD8+Foxp3+ Regulatory T Cells and Suppress Th2 Immune Responses during Allergen Immunotherapy. *The Journal of Immunology*. 2010; 184:7229–37. [PubMed: 20483759]
107. Ibanez AE, Smaldini P, Coria LM, Delpino MV, Pacifico LG, Oliveira SC, et al. Unlipidated outer membrane protein Omp16 (U-Omp16) from *Brucella* spp. as nasal adjuvant induces a Th1 immune response and modulates the Th2 allergic response to cow's milk proteins. *PLoS One*. 2013; 8:e69438. [PubMed: 23861971]
108. Bae MJ, Shin HS, Kim EK, Kim J, Shon DH. Oral administration of chitin and chitosan prevents peanut-induced anaphylaxis in a murine food allergy model. *Int J Biol Macromol*. 2013; 61:164–8. [PubMed: 23806320]
109. Smarr CB, Hsu C-L, Byrne AJ, Miller SD, Bryce PJ. Antigen-Fixed Leukocytes Tolerize Th2 Responses in Mouse Models of Allergy. *The Journal of Immunology*. 2011; 187:5090–8. [PubMed: 21976774]
110. Turley DM, Miller SD. Peripheral Tolerance Induction Using Ethylenecarbodiimide-Fixed APCs Uses both Direct and Indirect Mechanisms of Antigen Presentation for Prevention of Experimental Autoimmune Encephalomyelitis. *The Journal of Immunology*. 2007; 178:2212–20. [PubMed: 17277126]
111. Lambrecht BN, Hammad H. Allergens and the airway epithelium response: Gateway to allergic sensitization. *J Allergy Clin Immunol*. 2014; 134:499–507. [PubMed: 25171864]
112. Salazar F, Ghaemmaghami AM. Allergen recognition by innate immune cells: critical role of dendritic and epithelial cells. *Front Immunol*. 2013; 4:356. [PubMed: 24204367]
113. Soumelis V, Reche PA, Kanzler H, Yuan W, Edward G, Homey B, et al. Human epithelial cells trigger dendritic cell-mediated allergic inflammation by producing TSLP. *Nat Immunol*. 2002; 3:673–80. [PubMed: 12055625]
114. Rosenwasser LJ, Meng J. Anti-CD23. *Clin Rev Allergy Immunol*. 2005; 29:61–72. [PubMed: 16222084]
115. Kaiserlian D, Lachaux A, Grosjean I, Graber P, Bonnefoy JY. Intestinal epithelial cells express the CD23/Fc epsilon RII molecule: enhanced expression in enteropathies. *Immunology*. 1993; 80:90–5. [PubMed: 8244467]
116. Tu Y, Salim S, Bourgeois J, Di Leo V, Irvine EJ, Marshall JK, et al. CD23-mediated IgE transport across human intestinal epithelium: inhibition by blocking sites of translation or binding. *Gastroenterology*. 2005; 129:928–40. [PubMed: 16143132]
117. Li H, Nowak-Wegrzyn A, Charlop-Powers Z, Shreffler W, Chehade M, Thomas S, et al. Transcytosis of IgE-antigen complexes by CD23a in human intestinal epithelial cells and its role in food allergy. *Gastroenterology*. 2006; 131:47–58. [PubMed: 16831589]
118. Gould HJ, Sutton BJ. IgE in allergy and asthma today. *Nat Rev Immunol*. 2008; 8:205–17. [PubMed: 18301424]
119. Eiwegger T, Akdis CA. IL-33 links tissue cells, dendritic cells and Th2 cell development in a mouse model of asthma. *European Journal of Immunology*. 2011; 41:1535–8. [PubMed: 21618506]
120. Noti M, Wojno ED, Kim BS, Siracusa MC, Giacomini PR, Nair MG, et al. Thymic stromal lymphopoietin-elicited basophil responses promote eosinophilic esophagitis. *Nat Med*. 2013; 19:1005–13. [PubMed: 23872715]
121. Sherrill JD, Gao PS, Stucke EM, Blanchard C, Collins MH, Putnam PE, et al. Variants of thymic stromal lymphopoietin and its receptor associate with eosinophilic esophagitis. *J Allergy Clin Immunol*. 2010; 126:160–5.e3. [PubMed: 20620568]
122. Noti M, Kim BS, Siracusa MC, Rak GD, Kubo M, Moghaddam AE, et al. Exposure to food allergens through inflamed skin promotes intestinal food allergy through the thymic stromal lymphopoietin-basophil axis. *J Allergy Clin Immunol*. 2014; 133:1390–9. 9.e1–6. [PubMed: 24560412]

123. Roan F, Bell BD, Stoklasek TA, Kitajima M, Han H, Ziegler SF. The multiple facets of thymic stromal lymphopoietin (TSLP) during allergic inflammation and beyond. *J Leukoc Biol.* 2012; 91:877–86. [PubMed: 22442496]
124. Gauvreau GM, O'Byrne PM, Boulet LP, Wang Y, Cockcroft D, Bigler J, et al. Effects of an anti-TSLP antibody on allergen-induced asthmatic responses. *N Engl J Med.* 2014; 370:2102–10. [PubMed: 24846652]
125. Muto T, Fukuoka A, Kabashima K, Ziegler SF, Nakanishi K, Matsushita K, et al. The role of basophils and proallergic cytokines, TSLP and IL-33, in cutaneously sensitized food allergy. *Int Immunol.* 2014; 26:539–49. [PubMed: 24860117]
126. Yang Z, Sun R, Grinchuk V, Fernandez-Blanco JA, Notari L, Bohl JA, et al. IL-33-induced alterations in murine intestinal function and cytokine responses are MyD88, STAT6, and IL-13 dependent. *Am J Physiol Gastrointest Liver Physiol.* 2013; 304:G381–9. [PubMed: 23257921]
127. Johnston LK, Chien KB, Bryce PJ. The immunology of food allergy. *J Immunol.* 2014; 192:2529–34. [PubMed: 24610821]
128. Li D, Guabiraba R, Besnard A-G, Komai-Koma M, Jabir MS, Zhang L, et al. IL-33 promotes ST2-dependent lung fibrosis by the induction of alternatively activated macrophages and innate lymphoid cells in mice. *Journal of Allergy and Clinical Immunology.*
129. Kim YH, Yang TY, Park CS, Ahn SH, Son BK, Kim JH, et al. Anti-IL-33 antibody has a therapeutic effect in a murine model of allergic rhinitis. *Allergy.* 2012; 67:183–90. [PubMed: 22050307]
130. Liu X, Li M, Wu Y, Zhou Y, Zeng L, Huang T. Anti-IL-33 antibody treatment inhibits airway inflammation in a murine model of allergic asthma. *Biochem Biophys Res Commun.* 2009; 386:181–5. [PubMed: 19508862]
131. Wu LC, Scheerens H. Targeting IgE production in mice and humans. *Current Opinion in Immunology.* 2014; 31:8–15. [PubMed: 25156315]
132. Nadeau KC, Schneider LC, Hoyte L, Borrás I, Umetsu DT. Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. *Journal of Allergy and Clinical Immunology.* 2011; 127:1622–4. [PubMed: 21546071]
133. Sampson HA, Leung DYM, Burks AW, Lack G, Bahna SL, Jones SM, et al. A phase II, randomized, double-blind, parallel-group, placebo-controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy. *Journal of Allergy and Clinical Immunology.* 2011; 127:1309–10.e1. [PubMed: 21397314]
134. Rafi A, Do LT, Katz R, Sheinkopf LE, Simons CW, Klaustermeyer W. Effects of omalizumab in patients with food allergy. *Allergy and Asthma Proceedings.* 2010; 31:76–83. [PubMed: 20167148]
135. Schneider LC, Rachid R, LeBovidge J, Blood E, Mittal M, Umetsu DT. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. *Journal of Allergy and Clinical Immunology.* 2013; 132:1368–74. [PubMed: 24176117]
136. Liu J, Lester P, Builder S, Shire SJ. Characterization of Complex Formation by Humanized Anti-IgE Monoclonal Antibody and Monoclonal Human IgE. *Biochemistry.* 1995; 34:10474–82. [PubMed: 7654701]
137. Holgate S, Smith N, Massanari M, Jimenez P. Effects of omalizumab on markers of inflammation in patients with allergic asthma. *Allergy.* 2009; 64:1728–36. [PubMed: 19839977]
138. Beck LA, Marcotte GV, MacGlashan D Jr, Togias A, Saini S. Omalizumab-induced reductions in mast cell FcεRI expression and function. *Journal of Allergy and Clinical Immunology.* 2004; 114:527–30. [PubMed: 15356552]
139. Lin H, Boesel KM, Griffith DT, Prussin C, Foster B, Romero FA, et al. Omalizumab rapidly decreases nasal allergic response and FcεRI on basophils. *Journal of Allergy and Clinical Immunology.* 2004; 113:297–302. [PubMed: 14767445]
140. Prussin C, Griffith DT, Boesel KM, Lin H, Foster B, Casale TB. Omalizumab treatment downregulates dendritic cell FcεRI expression. *Journal of Allergy and Clinical Immunology.* 2003; 112:1147–54. [PubMed: 14657874]

141. Schroeder JT, Bieneman AP, Chichester KL, Hamilton RG, Xiao H, Saini SS, et al. Decreases in human dendritic cell-dependent TH2-like responses after acute in vivo IgE neutralization. *Journal of Allergy and Clinical Immunology*. 2010; 125:896–901.e6. [PubMed: 20132969]
142. Chang TW. The pharmacological basis of anti-IgE therapy. *Nat Biotech*. 2000; 18:157–62.
143. Chang TW, Chen J-B, Chu C-Y. The pharmacological mechanisms of omalizumab in patients with very high IgE levels—Clues from studies on atopic dermatitis. *Dermatologica Sinica*. 2012; 30:147–53.
144. Maselli DJ, Singh H, Diaz J, Peters JI. Efficacy of omalizumab in asthmatic patients with IgE levels above 700 IU/mL: a retrospective study. *Annals of Allergy, Asthma & Immunology*. 2013; 110:457–61.
145. Arm JP, Bottoli I, Skerjanec A, Floch D, Groenewegen A, Maahs S, et al. Pharmacokinetics, pharmacodynamics and safety of QGE031 (ligelizumab), a novel high-affinity anti-IgE antibody, in atopic subjects. *Clinical & Experimental Allergy*. 2014; 44:1371–85. [PubMed: 25200415]
146. MacGlashan DW Jr. Relationship between spleen tyrosine kinase and phosphatidylinositol 5' phosphatase expression and secretion from human basophils in the general population. *Journal of Allergy and Clinical Immunology*. 2007; 119:626–33. [PubMed: 17336612]
147. Cooper AM, Hobson PS, Jutton MR, Kao MW, Drung B, Schmidt B, et al. Soluble CD23 Controls IgE Synthesis and Homeostasis in Human B Cells. *The Journal of Immunology*. 2012; 188:3199–207. [PubMed: 22393152]
148. Poole JA, Meng J, Reff M, Spellman MC, Rosenwasser LJ. Anti-CD23 monoclonal antibody, lumiliximab, inhibited allergen-induced responses in antigen-presenting cells and T cells from atopic subjects. *Journal of Allergy and Clinical Immunology*. 2005; 116:780–8. [PubMed: 16210051]
149. Nakamura T, Kloetzer WS, Brams P, Hariharan K, Chamat S, Cao X, et al. In vitro IgE inhibition in B cells by anti-CD23 monoclonal antibodies is functionally dependent on the immunoglobulin Fc domain. *Int J Immunopharmacol*. 2000; 22:131–41. [PubMed: 10684997]
150. Zhou M, Du D, Zhao K, Zheng C. In vivo intranasal anti-CD23 treatment inhibits allergic responses in a murine model of allergic rhinitis. *Journal of Molecular Histology*. 2013; 44:327–38. [PubMed: 23377922]
151. Rosenwasser LJ, Busse WW, Lizambri RG, Olejnik TA, Totoritis MC. Allergic asthma and an anti-CD23 mAb (IDEC-152): results of a phase I, single-dose, dose-escalating clinical trial. *J Allergy Clin Immunol*. 2003; 112:563–70. [PubMed: 13679816]
152. Peng C, Davis FM, Sun LK, Liou RS, Kim YW, Chang TW. A new isoform of human membrane-bound IgE. *The Journal of Immunology*. 1992; 148:129–36. [PubMed: 1727861]
153. Brightbill HD, Jeet S, Lin Z, Yan D, Zhou M, Tan M, et al. Antibodies specific for a segment of human membrane IgE deplete IgE-producing B cells in humanized mice. *The Journal of Clinical Investigation*. 2010; 120:2218–29. [PubMed: 20458139]
154. Chen J-B, Wu PC, Hung AF-H, Chu C-Y, Tsai T-F, Yu H-M, et al. Unique Epitopes on CemX in IgE-B Cell Receptors Are Potentially Applicable for Targeting IgE-Committed B Cells. *The Journal of Immunology*. 2010; 184:1748–56. [PubMed: 20083663]
155. Gauvreau GM, Harris JM, Boulet L-P, Scheerens H, Fitzgerald JM, Putnam WS, et al. Targeting membrane-expressed IgE B cell receptor with an antibody to the M1 prime epitope reduces IgE production. *Science Translational Medicine*. 2014; 6:243ra85.
156. Jackman J, Chen Y, Huang A, Moffat B, Scheer JM, Leong SR, et al. Development of a Two-part Strategy to Identify a Therapeutic Human Bispecific Antibody That Inhibits IgE Receptor Signaling. *Journal of Biological Chemistry*. 2010; 285:20850–9. [PubMed: 20444694]
157. Eggel A, Buschor P, Baumann MJ, Amstutz P, Stadler BM, Vogel M. Inhibition of ongoing allergic reactions using a novel anti-IgE DARPIn-Fc fusion protein. *Allergy*. 2011; 66:961–8. [PubMed: 21272035]
158. Terada T, Zhang K, Belperio J, Londhe V, Saxon A. A chimeric human-cat Fcγ-Fel d1 fusion protein inhibits systemic, pulmonary, and cutaneous allergic reactivity to intratracheal challenge in mice sensitized to Fel d1, the major cat allergen. *Clinical Immunology*. 2006; 120:45–56. [PubMed: 16473552]

159. Zhu D, Kepley CL, Zhang K, Terada T, Yamada T, Saxon A. A chimeric human-cat fusion protein blocks cat-induced allergy. *Nat Med*. 2005; 11:446–9. [PubMed: 15793580]
160. Liu Y, Sun Y, Chang L-J, Li N, Li H, Yu Y, et al. Blockade of peanut allergy with a novel Ara h 2-Fc γ fusion protein in mice. *Journal of Allergy and Clinical Immunology*. 2013; 131:213–21.e5. [PubMed: 23199607]
161. Wambre E, DeLong JH, James EA, Torres-Chinn N, Pfützner W, Möbs C, et al. Specific immunotherapy modifies allergen-specific CD4+ T-cell responses in an epitope-dependent manner. *Journal of Allergy and Clinical Immunology*. 2014; 133:872–9.e7. [PubMed: 24373351]
162. Burton OT, Logsdon SL, Zhou JS, Medina-Tamayo J, Abdel-Gadir A, Noval Rivas M, et al. Oral immunotherapy induces IgG antibodies that act through Fc γ RIIb to suppress IgE-mediated hypersensitivity. *Journal of Allergy and Clinical Immunology*. 2014
163. Smith LD, Leatherbarrow RJ, Spivey AC. Development of small molecules to target the IgE:FceRI protein–protein interaction in allergies. *Future Medicinal Chemistry*. 2013; 5:1423–35. [PubMed: 23919552]
164. Kim B, Eggel A, Tarchevskaya SS, Vogel M, Prinz H, Jardetzky TS. Accelerated disassembly of IgE-receptor complexes by a disruptive macromolecular inhibitor. *Nature*. 2012; 491:613–7. [PubMed: 23103871]
165. Eggel A, Baravalle G, Hobi G, Kim B, Buschor P, Forrer P, et al. Accelerated dissociation of IgE-FceRI complexes by disruptive inhibitors actively desensitizes allergic effector cells. *Journal of Allergy and Clinical Immunology*. 2014; 133:1709–19.e8. [PubMed: 24642143]
166. Burton Oliver T, Noval Rivas M, Zhou Joseph S, Logsdon Stephanie L, Darling Alanna R, Koleoglou Kyle J, et al. Immunoglobulin E Signal Inhibition during Allergen Ingestion Leads to Reversal of Established Food Allergy and Induction of Regulatory T Cells. *Immunity*. 2014; 41:141–51. [PubMed: 25017467]
167. Strait RT, Morris SC, Yang M, Qu X-W, Finkelman FD. Pathways of anaphylaxis in the mouse. *Journal of Allergy and Clinical Immunology*. 2002; 109:658–68. [PubMed: 11941316]
168. Khodoun MV, Kucuk ZY, Strait RT, Krishnamurthy D, Janek K, Lewkowich I, et al. Rapid polyclonal desensitization with antibodies to IgE and FceRI α . *Journal of Allergy and Clinical Immunology*. 2013; 131:1555–64.e7. [PubMed: 23632296]

Figure 1. Oral tolerance

In oral tolerance, antigen is recognized by the immune system, but does not induce adverse immune reactions. Dendritic cells (DC) sample luminal contents, recognize antigen and traffic to lymph nodes. Activated tolerogenic DCs and macrophages secrete regulatory mediators like IL-10, TGF- β , and retinoic acid. Tolerogenic DCs migrate to the lymph node to present antigens to naive T lymphocytes (Th0) and promote differentiation of regulatory T (Treg) cells. Tregs secrete IL-10 and reduce effector CD4⁺ and CD8⁺ T cell responses.

Figure 2. Breakdown of tolerance

Allergy is associated with a breakdown in tolerance that promotes antigen sensitization. Increased epithelial cell permeability permits access of allergens to the underlying mucosa. Epithelial cells produce cytokines like TSLP, IL-33, and IL-25 that skew dendritic cell (DC) phenotype, activate innate lymphoid cells, and promote type 2 (Th2) immunity. DCs recognize food antigen and migrate to the lymph node, where they present allergens to naive T lymphocytes (Th0) in the presence of Th2-polarizing mediators (like IL-4) to promote the development of Th2 lymphocytes. Th2 lymphocytes secrete additional type 2 cytokines (IL-4, IL-5 and IL-13) and promote B cell isotype switching and IgE production. IgE binds to FcεRI/II receptors expressed by cells like mast cells and basophils to promote inflammatory allergic responses.

Figure 3. Early and late phase anaphylaxis

Anaphylactic reactions to allergens occur as an early and a late phase. In the early phase, IgE-allergen complexes are recognized by FcεRI/II expressed by cells like mast cells and basophils. Activation through FcεRI/II promotes the release of preformed mediators such as platelet activating factor (PAF), histamine, cytokines and chemokines, leukotrienes and proteases. These mediators induce immediate anaphylactic symptoms, including vasodilation, vascular permeability, and bronchoconstriction, and promote leukocyte recruitment from circulation. During the late phase reaction, recruited leukocytes, including basophils, eosinophils, T lymphocytes and monocytes/macrophages produce inflammatory cytokines, proteases and cytotoxic mediators that can damage tissue and induce anaphylactic symptoms.

Table 1

Potential biologics for the treatment of food allergies

Treatment	Drug/Agent	Company	Mechanism	Development
Omalizumab (Xolair)	Anti-IgE mAb	Genentech GlaxoSmithKline	Reduces free plasma IgE, prevents IgE binding to FcεRI/II	FDA approved for allergic asthma and chronic urticaria, several Phase I/II/III/IV
QGE031 (ligelizumab)	Anti-IgE mAb	Novartis	Reduces free plasma IgE, prevents IgE binding to FcεRI/II	Phase I/II
IgGγ1 Fc region allergen fusion	Anti-FcγRIIb, Anti-IgE	N/A	Crosslinks FcγRIIb to inhibit downstream IgE signaling	N/A
Quilizumab	Anti-M1'	Genentech	Binds to IgE-expressing B cells and induces apoptosis	Phase II
Lumiliximab	Anti-CD23	Biogen	Blocks CD23, reducing IgE production and transport	Phase I
DARPin (E2_79, bi53_79)	Analog targeting IgE-FcεRI interaction	N/A	High affinity disruptor of IgE binding to FcεRI	N/A
Mepolizumab (Bosatria)	Anti-IL-5 mAb	GlaxoSmithKline	Blocks IL-5	Phase III
Reslizumab (Cinquil)	Anti-IL-5 mAb	Teva Pharmaceuticals	Blocks IL-5	Phase II/III
Benralizumab	anti-IL-5Rα	MedImmune	Blocks IL-5 binding to IL-5Rα	Phase II/III
AMG-317	Anti IL-4Rα mAb	Amgen	Blocks binding of IL-4 and IL-13 to IL-4Rα	Phase II
Dupilumab	Anti IL4-Rα mAb	Regeneron Pharmaceuticals	Blocks IL-4 and IL-13 binding to IL-4Rα	Phase II/III
Lebrikizumab	Anti-IL-13	Genentech	Blocks IL-13	Phase II/III
Tralokinumab	Anti-IL-13	Cambridge Antibody Technology	Blocks IL-13	Phase II/III
AMG-157	Anti-TSLP	Amgen	Blocks TSLP	Phase I/II
AIC (CpG conjugated to Amb a 1)	TLR-9 agonist (adjuvant)	NIH Immune Tolerance Network	Stimulates TLR-9 and Th1 responses during ragweed IT	Phase II
R848 (Resiquimod)	TLR-7 agonist	N/A	Stimulates TLR-7 and promotes Th1 responses	N/A
Monophosphoryl Lipid A (MPL)	TLR-4 agonist (adjuvant)	Allergy Therapeutics	Stimulates TLR-4 and promotes Th1 responses	Phase II
OMP-16	Unlipidated outer membrane protein from <i>Brucella</i>	N/A	Broadly polarizes Th1 responses	N/A
Chitin / Chitosan	N/A	Universidade do Porto	Promotes Th1 responses	Phase II

Abbreviations: IT (immunotherapy), TSLP (thymic stromal lymphopoietin) TLR (toll-like receptor).