

# Therapeutics in Food Allergy: The Current State of the Art

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**Abstract** Food allergy is an increasing public health dilemma in Westernized countries, yet no viable treatments are currently available for those who are afflicted. The only options available for patients with food allergies are prevention of reactions by strict avoidance of the offending food(s) and symptomatic treatment of any adverse effects from accidental exposures. Approaches are being pursued to develop treatments, and allergen-specific therapies such as oral immunotherapy, sublingual immunotherapy, and epicutaneous immunotherapy with different foods have shown promise. Other modalities are also being investigated, potentially leading to the discovery of novel therapeutic options.

**Keywords** Food allergy · Treatment · IgE-mediated · Oral immunotherapy · Sublingual immunotherapy · Epicutaneous immunotherapy

## Introduction

Food allergy is a condition in which individuals develop a specific immunologic response that occurs reproducibly on exposure to a given food. In IgE-mediated food allergy, IgE antibodies bind to high-affinity IgE receptors on mast cells

and basophils, and when exposed to the sensitizing proteins, activate these cells to release potent mediators that cause symptoms such as hives, swelling, wheezing, and vomiting, which are features of allergic reactions [1•]. However, the underlying mechanism leading to initial sensitization has yet to be fully elucidated. Multiple factors, including the dose and route of first exposure to food allergens, are particularly important in the development of tolerance versus sensitization.

In recent years, the prevalence of food allergy in Westernized countries has increased [1•]. Gupta and colleagues [2] report that adverse immune reactions to foods occur in 8% of young children in the United States. This is an increase of almost 20% over the past decade [3]. However, there is also a concomitant increase in public awareness of food allergies, as up to 35% of individuals self-report having a food allergy; true food allergy, though, is confirmed in only a small percentage of patients when actual food challenges are performed [4]. A small number of foods account for most reported IgE-mediated food allergic reactions: milk, egg, wheat, soy, peanut, tree nuts, fish, and shellfish. The major food allergens are varied but do have several similar physical properties. Allergic molecules tend to be small, water-soluble glycoproteins derived from animal or plant sources and are resistant to heat, acidic environments, and proteases [5].

The current standard of care for individuals affected with food allergy is extremely limited. Management is based on establishing a correct diagnosis; preventing accidental exposures; and swift, effective treatment of allergic symptoms. Strict avoidance of the culprit food and the use of auto-injectable epinephrine (for intramuscular injection) and diphenhydramine are paramount for those afflicted. Unfortunately, accidental exposures leading to fatalities still occur; thus, a need for effective therapy remains vital. Novel

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therapeutic advances to combat food allergy can be classified into one of two categories: allergen specific and non-allergen specific. The approaches discussed in this article include the use of oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT). Each of these methods is allergen specific and designed either to alter the allergic response to specific food allergens in order to mitigate the level of sensitization (desensitization), thus lowering the risk and/or severity of food-related, IgE-mediated reactions, or to induce long-term tolerance. In addition, non-allergen-specific methods primarily serve to downregulate the allergic immune response, and these modalities of therapy are also discussed. A brief review of oral tolerance is first provided, and guideline recommendations for the prevention of food allergy are briefly discussed, as there may be a crucial time period in infancy to induce tolerance to certain foods.

### Pathogenesis: Development of Oral Tolerance

Food allergy is a result of pathologic reactions to common dietary antigens and has a complex pathogenesis. Disruption in the homeostasis between the gut immune system and dietary antigens occurs as physiologic and immunologic barriers are disturbed. This condition manifests in the setting of appropriate genetic risk factors, intrinsic properties of dietary antigens, and other environmental factors. Under typical circumstances, the gut immune system, the largest immune organ in the body, is relatively hyporesponsive to food antigens. This state of tolerance is maintained by several mechanisms, including the integrity of gut epithelium to minimize absorption of allergens and the presence of tolerogenic immune cells. It is thought that the development of IgE-mediated hypersensitivity reactions occurs as food antigens are presented by antigen-presenting cells such as dendritic cells in the gut mucosa. Evidence exists that dendritic cells and macrophages in the intestine play a critical role in arbitrating mucosal tolerance against commensal organisms and dietary antigens while mounting inflammatory responses against harmful pathogens [6]. Consequently, otherwise benign food allergens, in the correct environment, can cause severe reactions in those primed for developing food allergies.

The most significant component of the physical barriers in the gastrointestinal system is the intact columnar epithelial cells that occur in a single layer joined together by gap junctions. These cells barricade the sterile internal environment from the outside environment. Their main function is to absorb nutrients from ingested foods while preventing pathogens from entering the circulation. A mucus layer covers the gut epithelium and functions to trap foreign pathogens.

Characteristics of the gastrointestinal system, such as the acidic pH, bioactive enzymes, and bile acids, are all important components that help neutralize offending pathogens and render allergens less immunogenic [7].

The innate and the adaptive immune system play significant roles in the development of oral and gastrointestinal tolerance. The innate immune system includes immune cells (macrophages, neutrophils, and dendritic cells) that ingest foreign antigens and receptors (eg, Toll-like receptors) that are activated by bacterial products, such as from microorganisms in the gut, and modulate cellular function. The adaptive immune system includes cells (T and B lymphocytes), along with circulating antibodies such as IgG and IgE that specifically recognize foreign molecules. Specific cytokines such as interleukin (IL)-4 and IL-13 produced by immune cells direct the adaptive immune system to generate T cells called T-helper type 2 (Th2) cells that mount an IgE response [8].

### Therapeutics

#### Prevention

The current National Institute of Allergy and Infectious Diseases Guidelines for the Diagnosis and Management of Food Allergy provide recommendations for the prevention of food allergy [1•]. These guidelines state that there are insufficient data to suggest that maternal diet affects the development or the course of food allergy in the infant; thus, they do not support maternal diet restriction during pregnancy or lactation. The current recommendations are that all infants be exclusively breastfed for 4–6 months and that the introduction of solid foods (including potential allergens) should not be delayed beyond 4–6 months. In fact, emerging studies show that earlier introduction of the highly allergenic foods, such as milk and egg, may decrease the risk of these allergies [9–12].

#### Oral Immunotherapy

Initial OIT trials focused on egg and milk allergy. However, OIT currently as a therapeutic modality for the treatment of food allergy has been investigated with many food items (eg, egg, milk, peanut, fish, apple, orange, and celery). In this section, we discuss the most recent novel studies with OIT.

In 2009, an open-label, uncontrolled study of OIT to peanut proteins enrolled 39 children between the ages of 12 and 111 months for a 36-month trial in a gradual build-up phase followed by a maintenance phase [13]. Despite adverse reactions (92% in build-up phase), almost all participants completed the study and were able to ingest 3.9 g of peanut protein without adverse reactions. This is a

sufficient level to protect individuals from accidental exposure.

Most recently, a randomized, double-blind, placebo-controlled (DBPC) study was performed with peanut OIT to establish safety and effectiveness [14•]. Twenty-eight participants 1–16 years of age with a clinical history of reaction to peanut within 60 min of ingestion with a positive skin prick test (SPT) and ImmunoCAP (Phadia Thermo Fisher Scientific, Waltham, MA) were recruited in this multicenter trial and randomly assigned to active or placebo therapy. Nineteen received OIT with peanut flour, and nine received placebo over 44 weeks of dose escalation, followed by 4 weeks of maintenance phase. Participants underwent a DBPC food challenge (DBPCFC) at the 48th week. Eighty-four percent of participants (16 of 19) successfully completed 1 year of OIT treatment, and all 16 reaching the final oral food challenge (OFC) completed the 5,000-mg peanut protein OFC (20 peanuts), with only 1 requiring antihistamine therapy. This was compared with the placebo group, whose median cumulative dose was 280 mg (1 peanut) before the OFC was discontinued due to symptom development. Statistically significant changes were also seen in titrated SPTs, in which median wheal size decreased from 7 mm (range, 5–15 mm) to 1.75 mm (range, 0–10 mm), and the immunologic changes observed in antigen-specific immunoglobulins, mast cells, and T cells were comparable to what is typically seen with allergen immunotherapy and similar to the natural development of tolerance to food allergens.

There have been three randomized OIT trials to cow's milk (CM), including one DBPC randomized trial [15]. Twenty children 6–7 years of age were randomly assigned to receive milk OIT or placebo. All individuals in the active group who completed the protocol were able to tolerate a higher dose of CM (5,140 mg) compared with the placebo group (40 mg). It is not yet known whether these children were permanently tolerized, but in a follow-up open-label phase of this study, there was a continued decrease in rates of reaction with sustained milk exposure [16]. Adverse reactions still occurred frequently in an unpredictable manner; investigators saw reactions to a previously tolerated dose with exercise or with viral infections.

Most recently, a pilot phase 1 study in 11 children (7–11 years of age) with CM allergy was performed using omalizumab (monoclonal antibody against IgE) in combination with rapid oral desensitization [17•]. For children with IgE levels less than 700 kU/L, omalizumab was dosed according to the package insert, and for the three children with serum IgE levels greater than 700 kU/L, the dose was 225–300 mg (~0.016 mg/kg per IgE [12]) every 2–4 weeks. Nine weeks after the start of omalizumab treatment, oral CM desensitization was performed in two phases. Rush oral desensitization occurred on the first day of desensitization,

starting with 0.1 mg of milk powder, with doses increasing every 30 min to a maximum dose of 1,000 mg (cumulative dose, 1,992 mg). Nine of the 10 participants reached the 1,000-mg dose on the first day of desensitization, with one 1 receiving epinephrine after administration of the 1,000-mg dose for nasal obstruction and generalized urticaria refractory to diphenhydramine and cetirizine. Desensitization with daily doses of milk continued in the 10 participants, with weekly increases in the dose of milk over the next 7–11 weeks. During the study, individuals were asked to take the study milk dose on a full stomach and to halve the study milk dose during a viral infection. Nine of the 10 patients reached the maximum daily dose of 2,000 mg of milk (the primary end point of the study). The individual who received epinephrine during the rush phase of desensitization achieved a daily dose of 1,200 mg when the omalizumab was stopped (end of the weekly dose escalation phase, week 16). Omalizumab was discontinued at week 16, but the participants continued to ingest milk followed by a DBPCFC 8 weeks later. All nine patients passed the DBPCFC and an open challenge with greater than 8,000 mg/d of milk without symptoms. The safety data showed that at 24 weeks, 1.8% of total doses resulted in grade I symptoms, and 0.3% and 0.1% resulted in grade II and III symptoms, respectively. This was the first trial using omalizumab in the setting of OIT, and it shows that rapid oral desensitization with milk can be achieved with the additional use of omalizumab. This trial did not address whether these individuals are permanently tolerized, however, even with the discontinuation of ingestion of 8,000 mg/d of milk.

The mechanisms whereby OIT is effective and factors that may be responsible for the inability to achieve complete desensitization are under intense investigation. Several limitations and unknowns still exist with OIT, the most important being the difficulty faced in distinguishing the difference between the actual effects of OIT versus the natural resolution of food allergy, in which most children afflicted outgrow their allergy to egg and milk. Furthermore, some children cannot tolerate maintenance doses due to adverse reactions, and in most of these patients, daily sustained dosing is needed to maintain a desensitized state. There is also the added concern that in some of these children, adverse reactions have occurred in a previously tolerated dose that transpire in an unpredictable fashion.

### Sublingual Immunotherapy

SLIT, unlike OIT, involves the administration of micrograms to milligrams of allergen extract under the tongue, with subsequent spitting or swallowing of the dose after a set period of time. The safety and efficacy of SLIT with peanuts have been studied in 18 children (age 1–11 years) with

physician-documented clinical history reaction to peanuts within 60 min of ingestion, as well as SPT and ImmunoCAP positivity. In this DBPC study, participants underwent 6 months of dose escalation and 6 months of maintenance dosing followed by a DBPCFC [18•]. The participants were randomly assigned to placebo or crude peanut extract, which was held under then tongue for 2 min prior to swallowing. After 12 months of therapy, the active group was able to tolerate a dose 20-fold higher (1,710 mg vs 85 mg) than the placebo group. SPT wheal size was lower in the active group following SLIT. Moreover, similar to immunologic responses seen following aeroallergen subcutaneous immunotherapy, immunologic data demonstrated a diminished allergic response in mast cells and basophils, decreasing peanut-specific IgE and increasing peanut-specific IgG<sub>4</sub> levels, and a decrease in IL-5 levels. Unlike OIT, in which systemic adverse effects were common, individuals undergoing SLIT experienced predominantly localized oropharyngeal symptoms, with only 0.3% of the active doses requiring oral antihistamine.

A randomized DBPC trial of SLIT with peach extract was undertaken in 56 adults (18–56 years of age) with proven allergy after peach ingestion and positive SPT and ImmunoCAP [19]. Thirty-seven individuals were randomly assigned into the active arm, and 19 received placebo. DBPCFCs were done before the trial and 6 months following SLIT. After 6 months of SLIT, the investigators found that the active group tolerated higher amounts of peach—although the findings were not statistically significant—and demonstrated a significant decrease in SPT (5.3-fold) and a significant increase in IgE and IgG<sub>4</sub> to Pru p 3. The active group had significantly more frequent local reactions (threefold) compared with placebo, but there were no differences in the number of systemic reactions seen for both groups. The issue remains that perhaps a higher maintenance dose would have yielded significant results. Moreover, in a follow-up study, levels of allergens that cross-react with Pru p 3 were measured prior to the SLIT, 1 month after treatment, and 6 months after treatment [20]. The investigators found that at baseline, 83.3% of patients recognized recombinant (r)Pru p 3; 18.5% recognized rMal d 1 (apple); 24.1% rMal d 4; and 25.9% Art v 3 (artemis). During the follow-up phase, three individuals in the active arm developed new sensitizations to rMal d 1, rPru p 3, and rMal d4, each to a single allergen. This notion of the effect of food immunotherapy on other food- or pollen-related sensitization needs to be further investigated.

### Epicutaneous Immunotherapy

EPIT is an alternative therapy in which the allergen is delivered via an epicutaneous patch that contains

solubilized allergen and disseminates it into the stratum corneum. Epicutaneous vaccination specifically targets the outermost layer of the skin, the epidermis, which has properties ideal for delivery of allergen. The epidermis is a nonvascularized, multilayered epithelium that has potent immune surveillance exerted by keratinocytes and Langerhans cells. Antigen presentation to the local draining lymph nodes by skin dendritic cells has been shown to efficiently induce systemic IgM and IgG, as well as mucosal IgA responses [21]. Langerhans cells have been proposed as possible targets for vaccination, as they are crucial in the uptake of antigens and trigger downstream effects of inducing potent T-cell responses [22].

A pilot study was performed in 18 children (3 months–15 years of age) with physician-confirmed CM allergy and positive OFCs [23•]. Participants were randomly assigned to receive therapy with active epicutaneous delivery system or placebo by three 48-hour applications (1 mg skimmed milk powder or 1 mg glucose as placebo) for 3 months. At 3 months, the active group tolerated a mean of 23.61 mL, compared with 1.77 mL at baseline, whereas the cumulative tolerated dose did not change in the placebo-treated group. EPIT in this pilot study demonstrated few adverse reactions, as the most common side effects were local pruritus and eczema at the site of the patch. Milk-specific IgE levels were not altered from prior baseline compared with the IgE levels after 3 months of treatment.

Peanut EPIT has been successful in the murine model [24, 25]. A phase 1 trial is currently under way in the United States to evaluate the safety of peanut EPIT in peanut-sensitized individuals, and a phase 2 trial is under way in France. In the United States, work began in July 2010, with an estimated completion date of October 2011. This phase 1 study will look at peanut EPIT safety and tolerability in pediatric and adult populations with peanut allergy. Four doses of peanut proteins—20, 100, 250, and 500 µg—will be repeatedly delivered on the skin by dose escalation in consecutive cohorts of five individuals, starting with the lowest dose. In each cohort of five, four participants will receive peanut proteins and one will receive placebo in a blinded manner. For each dose, the peanut proteins will be applied on the skin every day or every other day. The total duration of the treatment for each individual is 2 weeks (<http://clinicaltrials.gov>). The phase 2 trial in France is a multicenter DBPC pilot protocol that began in August 2010, with an estimated study completion in December 2012. This study's primary outcome will be the proportion of individuals able to consume greater than 1,000 mg of peanut protein symptom free during the DBPCFC to peanut at 6 months, or who have a 10-fold increase in the quantity of peanut protein consumed as compared with baseline value.

### “Modified Oral Immunotherapy”: Baked Milk

OIT, SLIT, and EPIT as described above have been studied in facilities that allow for close monitoring during the initial phase or with escalation. Such close monitoring is not available to the majority of practicing allergists, who work in smaller practices. The prerequisite that food allergen desensitization occur in larger academic centers underscores the importance of developing a method of food allergy desensitization that can be performed safely by community allergists. Kim et al. [26] demonstrated that ingestion of baked milk accelerates the resolution of CM allergy in children. In this study, 89 children (median age, 6.6 years) with active milk allergy were enrolled. Over a median of 37 months (range, 8–75 months), 88 individuals were challenged to progressively less heated forms of milk at varying intervals. Thirty-nine of the 65 (60%) individuals initially tolerant to baked milk tolerated unheated milk, 18 (28%) tolerated baked milk/baked cheese, and 8 (12%) chose to strictly avoid milk. Among the baked milk–reactive subgroup ( $n=23$ ), two individuals (9%) could tolerate unheated milk, three (13%) tolerated baked milk/baked cheese, and most individuals remained intolerant. The severity of symptoms during OFC was low. Moreover, there was no increase in severity of the individuals’ other atopic conditions. A similar study had been performed previously with extensively heated egg [27]. This method of oral desensitization appears safe, inexpensive, and accepted by many patients. Community allergists can utilize such a method easily with minimal difficulty.

### Other Allergen-Specific Therapies

The use of a rectally administered vaccine that contains recombinant modified peanut proteins (EMP-123) Ara h 1, 2, and 3 completed a phase 1 trial in September 2011. This study evaluated the safety of a rectally administered product, EMP-123, consisting of three recombinant modified peanut protein antigens encapsulated within heat or phenol-killed *Escherichia coli*. EMP-123 is designed to act as an allergy vaccine with an eventual goal to induce tolerance to the major peanut proteins responsible for peanut allergy (<http://clinicaltrials.gov>).

Peptide immunotherapy with T-cell epitopes in which T cells are stimulated to predominantly Th2 responses without cross-linking IgE has been reported [28]. Multiple CD4<sup>+</sup> T-cell lines specific for major peanut allergen Ara h 2 were generated from peripheral blood mononuclear cells of 16 HLA-diverse peanut-allergic individuals. Five dominant epitopes were presented by *HLA-DP*, *HLA-DQ*, and *HLA-DR* and were recognized by T cells from all 16 individuals. Further manipulation of three short epitopes targeted Th2

cells directly without binding peanut-specific IgE. These novel Ara h 2 peptides could be used as novel candidates for a T-cell–targeted immunotherapy.

### Allergen-Nonspecific Modalities

The methods discussed above all aim to desensitize or tolerize against a particular allergen in a sensitized individual. Other advances aim to downregulate the allergic immune response in a more global fashion.

A multicenter clinical trial using humanized monoclonal anti-IgE murine IgG<sub>1</sub> antibody (TNX-901) in 84 peanut-allergic individuals was reported [29]. The individuals were randomly assigned to receive placebo or TNX-901 at three different doses. A significant increase in the threshold of sensitivity, but only in the high-dose group, was seen in the active group compared with placebo. Omalizumab, an anti-IgE humanized IgG<sub>1</sub> antibody that is different from TNX-901, is currently being studied in peanut-allergic individuals (<http://clinicaltrials.gov>). A previous clinical trial investigating the efficacy and safety of omalizumab was terminated early due to adverse events in two participants during the initial screening peanut challenge [30].

The use of the parasitic helminth *Trichuris suis* ova as a possible therapy for food allergy is also currently under investigation. This study is based on preliminary findings in a murine model of food allergy; helminth infection was protective against IgE sensitization and anaphylaxis [31]. Moreover, parasitic helminth infections can protect against allergic airway inflammation and modulate disease in ulcerative colitis, Crohn’s disease, and allergic rhinitis [32, 33, 34]. It is thought that lack of exposure, particularly during childhood, to naturally occurring pathogens has led to subtle changes in the human immune system, resulting in an increased propensity to develop allergic and autoimmune responses. This phase 1 study will assess whether *T. suis* ova is safe in adults and children with peanut or tree nut allergy.

Herbs have been used in traditional Chinese medicine for many centuries. Herbal medication is being evaluated for its potential therapeutic benefit in peanut allergy. In a murine model with Food Allergy Herbal Formula (FAHF)-1, a mixture of 11 herbs, protected mice with peanut allergy–induced anaphylaxis [35]. A phase 1 randomized DBPC study was recently completed and showed that FAHF-2 (simplified herbal formula containing 9 herbs) was safe and well-tolerated in 19 adults with peanut and tree nut allergies [36]. A phase 2 trial using FAHF-2 is in progress to evaluate the efficacy of FAHF-2 as well as to characterize the immunomodulatory effects of this herbal formula.

## Conclusions

Food allergy is an increasingly prevalent problem in Westernized countries, with no cure currently available for those who are afflicted. We have limited scope in understanding the risk factors predisposing individuals to food allergy, and novel treatments discussed above remain experimental. Allergen-specific therapies such as OIT, SLIT, and EPIT have largely been performed in academic centers, as safety remains a great concern. Thus, for many affected individuals, these therapeutic modalities are not readily available. Moreover, many approaches are labor intensive and not cost-effective. However, food immunotherapy is only in its infancy, and novel therapeutic approaches currently on the horizon, as well as those yet to be developed, provide hope for finding an effective therapy in the near future.

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