

# Future therapies for food allergies

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**Date of Original Release:** March 2011. Credit may be obtained for these courses until February 28, 2013.

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**Overall Purpose/Goal:** To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

**Target Audience:** Physicians and researchers within the field of allergic disease.

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### Activity Objectives

1. To summarize the current management and candidate therapies for IgE-mediated forms of food allergy.
2. To understand that allergen-specific immunotherapy can include feeding patients heat-treated allergen, as well as oral, sublingual, and epicutaneous immunotherapy.
3. To recognize that allergen-nonspecific therapy might include humanized monoclonal anti-IgE antibodies, Food Allergy Herbal Formula (FAHF) 1, probiotics, and Toll-like receptor agonists.
4. To review key clinical trials and studies in food allergy treatment.

**Recognition of Commercial Support:** This CME activity has not received external commercial support.

**Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations:** A. Nowak-Węgrzyn has declared that she has no conflict of interest. H. A. Sampson is a consultant for Allertein Therapeutics, LLC; has received research support from and is a consultant and scientific advisor for the Food Allergy Initiative and the National Institute of Allergy and Infectious Diseases/National Institutes of Health; is a medical advisor for the Food Allergy & Anaphylaxis Network; is a scientific advisor for the University of Nebraska FARRP; and is a 45% owner of Herbal Springs, LLC.

Food allergy is an increasingly prevalent problem in westernized countries, and there is an unmet medical need for an effective form of therapy. A number of therapeutic strategies are under investigation targeting foods that most frequently provoke severe IgE-mediated anaphylactic reactions (peanut, tree nuts, and shellfish) or are most common in children, such as cow's milk and hen's egg. Approaches being pursued are both food allergen specific and nonspecific. Allergen-specific approaches include oral, sublingual, and epicutaneous immunotherapy (desensitization) with native food allergens and mutated recombinant proteins, which have decreased IgE-binding activity, coadministered within heat-killed *Escherichia coli* to generate maximum immune response. Diets containing extensively heated (baked) milk and egg represent an alternative approach to food

oral immunotherapy and are already changing the paradigm of strict dietary avoidance for patients with food allergy. Nonspecific approaches include monoclonal anti-IgE antibodies, which might increase the threshold dose for food allergen in patients with food allergy, and a Chinese herbal formulation, which prevented peanut-induced anaphylaxis in a murine model and is currently being investigated in clinical trials. The variety of strategies for treating food allergy increases the likelihood of success and gives hope that accomplishing an effective therapy for food allergy is within reach. (*J Allergy Clin Immunol* 2011;127:558-73.)

**Key words:** Food allergy, oral immunotherapy, sublingual immunotherapy, probiotics, epicutaneous immunotherapy, desensitization, milk allergy, peanut allergy, egg allergy, anti-IgE, anti-IgE therapy, anti-IL-5 therapy

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Received for publication November 30, 2010; revised December 29, 2010; accepted for publication December 29, 2010.

Available online February 3, 2011.

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0091-6749/\$36.00

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doi:10.1016/j.jaci.2010.12.1098

Over the past 2 decades, food allergy has emerged as a major public health problem in westernized societies.<sup>1,2</sup> In American children younger than 18 years, the prevalence of food allergy has increased by 18% and the prevalence of peanut allergy has tripled (0.4% to 1.4%) from 1997 to 2008.<sup>3,4</sup> Food allergy is the most common cause of anaphylaxis evaluated in the emergency department in all age groups, and the number of hospitalizations for food-induced anaphylaxis has increased more than 3-fold in the past decade in the United States and United Kingdom.<sup>3,5,6</sup> Food-induced anaphylaxis occasionally results in fatalities, with

*Abbreviations used*

- DBPCFC: Double-blind, placebo-controlled food challenge
- EOE: Eosinophilic esophagitis
- EPIT: Epicutaneous immunotherapy
- FAHF: Food Allergy Herbal Formula
- FoxP3: Forkhead box protein 3
- HKE: Heat-killed *Escherichia coli*
- HKLM: Heat-killed *Listeria monocytogenes*
- ISS: Immunostimulatory sequence
- Man<sub>51</sub>-BSA: Mannoside-conjugated BSA
- OIT: Oral immunotherapy
- pDNA: Plasmid DNA
- PFAS: Pollen-food allergy syndrome
- SIGNR-1: C-type lectin receptor, also called CD209b
- SLIT: Sublingual immunotherapy
- TCM: Traditional Chinese medicine
- TLR9: Toll-like receptor 9

more than 90% of deaths in the United States caused by reactions to peanut or tree nuts.<sup>7,8</sup>

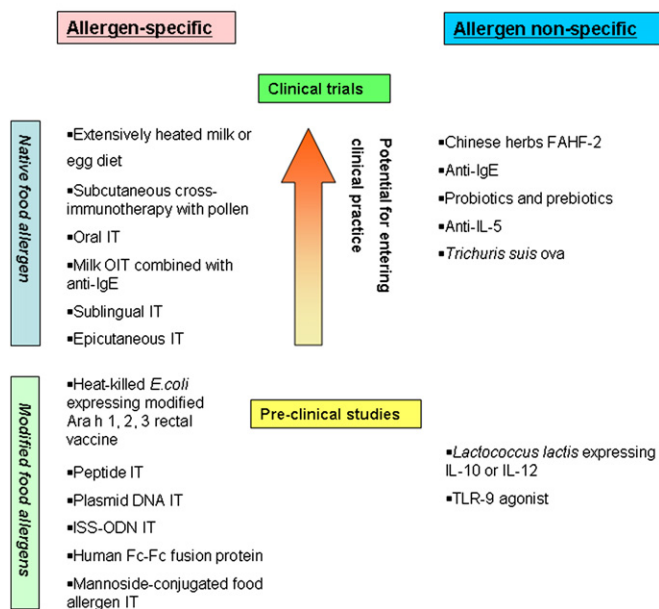
The current management of food allergy is limited to strict dietary avoidance, nutritional counseling, and emergency treatment of adverse reactions.<sup>9</sup> In this review we will focus on efforts to treat IgE-mediated forms of food allergy. Although attempts to desensitize patients with food allergy date back more than 100 years, such as oral immunotherapy (OIT),<sup>10</sup> there are no accepted therapies proved to accelerate the development of oral tolerance or to provide effective protection from unintentional exposures.<sup>1</sup> However, a number of therapeutic strategies are under investigation targeting foods that most frequently provoke severe IgE-mediated anaphylactic reactions (peanut, tree nuts, and shellfish) or are most common in children, such as cow's milk and hen's egg.<sup>11</sup> Approaches being pursued are both food allergen specific and nonspecific (Fig 1).<sup>12</sup> Allergen-specific approaches include OIT, sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT; desensitization) with native food allergens and mutated recombinant proteins, which have decreased IgE-binding activity, coadministered within heat-killed *Escherichia coli* (HKE) to generate maximum immune response. Diets containing extensively heated (baked) food, such as milk or egg, might represent an alternative approach to allergen-specific immunomodulation of food allergy in some patients.

Nonspecific approaches include anti-IgE mAbs, which might increase the threshold dose for reactivity to food allergens, and a Chinese herbal formulation, which prevented peanut-induced anaphylaxis in a murine model of peanut-induced anaphylaxis and is currently being investigated in clinical trials.

**SELECTION OF CANDIDATES FOR NOVEL FOOD ALLERGY THERAPIES**

Food allergies seriously alter the quality of life of patients with food allergy and their families. Fortunately, about 85% of children allergic to foods such as cow's milk, egg, wheat and other cereal grains, and soy "outgrow" (develop tolerance) their allergy, whereas only 15% to 20% of children allergic to peanut, tree nuts, fish, and shellfish will show spontaneous tolerance. Diagnostic tests are needed that can distinguish subjects with

**FOOD ALLERGY THERAPY**



**FIG 1.** Approaches to food allergy immunotherapy. ISS-ODN, Immunostimulatory oligodeoxynucleotide; IT, immunotherapy.

transient from persistent forms of food allergy so that therapeutic strategies can be used early to accelerate the induction of tolerance in those who can outgrow their allergy or to induce tolerance in those with the persistent form. Currently, there are no diagnostic tests (eg, serum food allergen-specific IgE antibody measurement or skin prick tests) that reliably predict the potential for spontaneous development of oral tolerance. However, 2 recent reports in children with multiple food allergies noted that few children with peak cow's milk- or egg white-specific IgE antibody levels of 50 kU<sub>A</sub>/L or greater (UniCAP; Phadia, Uppsala, Sweden) outgrow their allergy by their late teenage years.<sup>13,14</sup> In addition, recent studies using peptide microarray assays to determine the diversity and affinity of IgE binding to sequential epitopes on major food allergens (eg, peanut, cow's milk, and egg white) might be useful in determining the severity and persistence of food allergy in affected patients (Table I).<sup>15-23</sup>

**IMMUNOTHERAPEUTIC APPROACHES FOR TREATING FOOD ALLERGY**

Patients with food allergy can be divided into 3 basic phenotypes: transient food allergy, persistent food allergy, and food-pollen (oral allergy) syndrome. Based on developing evidence, it appears that each of these forms of IgE-mediated food allergy is the result of different immunologic mechanisms and therefore is likely to require different immunotherapeutic approaches to bring about resolution.

It appears that patients with transient food allergy will have the most favorable response to therapy. Although it might be argued that transient food allergy does not require treatment, the potential benefits of therapy include accelerated development of tolerance and improved quality of life and nutrition.

Persistent food allergy might present a more challenging situation. Patients with the persistent form of food allergy are

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