

Towards immunotherapy for peanut allergy

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Purpose of review

Food allergy is a major cause of life-threatening hypersensitivity reactions. Peanut allergy is the most serious of the hypersensitivity reactions to foods due to its persistence and high risk of severe anaphylaxis. Currently, strict avoidance of the allergenic food and ready access to self-injectable epinephrine is the 'standard of care' for food allergy. Based on extensive characterization of food allergens and a better understanding of the immunological mechanisms underlying allergic disease, promising therapeutic modalities for food allergy treatment and prevention are being developed.

Recent findings

Immunotherapeutic strategies include peptide immunotherapy, mutated protein immunotherapy and DNA immunization, which all strive to decrease the deleterious Th2 response. Another approach already in clinical trials for peanut allergy is the anti-IgE therapy which prevents circulating IgE from binding to effector cells, consequently decreasing clinical symptoms after peanut ingestion. In order to be applicable, these strategies must be well tolerated, inexpensive and easily administered. Realistic treatment options would likely involve a combination of different approaches.

Summary

Food allergy affects approximately 4–6% of children and 3–4% of adults. Peanut allergy can be devastating as reactions range from urticaria to severe anaphylactic shock and death. The only preventive measure for peanut allergy is strict avoidance of the incriminating food. It is likely immunotherapy will be available in the near future as a well tolerated and effective therapy for treating peanut allergy. The use of the anti-IgE therapy in conjunction with other immunotherapy would possibly be the best treatment option in the future.

Keywords

allergen-specific immunotherapy, anti-IgE immunotherapy, DNA immunization, food allergy, immunostimulatory sequences, mutated allergen, peanut hypersensitivity, soybean homologous proteins, T-cell reactive peptide

Abbreviations

APCs	antigen presenting cells
IgE	Immunoglobulin E
ISS	immunostimulatory sequences

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Introduction

Food allergy is a major cause of life-threatening hypersensitivity reactions, with peanut allergy the most serious of the hypersensitivity reactions to foods due to its persistence and high risk of severe anaphylaxis. Unfortunately, at the present time, strict avoidance of the allergenic food and ready access to self-injectable epinephrine is the only available treatment for food allergy. Based on recent studies of food allergens and a better appreciation of the immunological mechanisms underlying allergic disease, potential therapeutic modalities for the treatment and eventual prevention of food allergy are being developed.

Traditional therapies

Immunotherapy for IgE-mediated disease has been used since its first description nearly a century ago [1]. Although injection immunotherapy has traditionally been employed in the treatment of inhalant allergies, such as allergic rhinitis, it has also been used with success in the treatment of food allergy. Injection immunotherapy was first used in the treatment of food allergy when a young child was successfully desensitized to fish [2]. In patients with allergic rhinitis experiencing oral allergy symptoms after ingestion of cross-reacting allergens present in fresh fruits, nuts and vegetables, traditional injection immunotherapy has also been successful in many cases in ameliorating the oral allergy symptoms with minimal adverse reactions [3–6].

Traditional injection immunotherapy for food allergy is currently not recommended because of the allergic side-effects of the therapy [7]. Studies have been conducted in a double-blind, placebo-controlled trial of rush immunotherapy for the treatment of anaphylactic hypersensitivity to peanuts [8]. Patients in the treatment group were able to tolerate increased amounts of peanuts in food challenges after treatment. Unfortunately, an unacceptably high rate of adverse systemic reactions was associated with the rush immunotherapy and maintenance protocols [8,9]. The actual peanut immunotherapy produced

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Table 1. Potential immunotherapeutic strategies for the treatment of peanut allergy.

Therapy	Type of allergy	Route	Immunologic mechanism	Risk*
Traditional injection immunotherapy	Oral Allergy Syndrome	Subcutaneous	Immune deviation from Th2 to Th1, increased IgG-blocking antibodies, decreases specific-IgE	Safe, when performed properly
Peptide immunotherapy	IgE-mediated food allergy	Subcutaneous	Immune deviation from Th2 to Th1	Appears safe
Traditional Chinese Medicine	IgE-mediated food allergy (asthma)	Subcutaneous	Immune deviation from Th2 to Th1	Appears safe
Mutated protein immunotherapy	IgE-mediated food allergy	Subcutaneous, intranasal and oral	Immune deviation from Th2 to Th1 (?)	Appears safe
Homologous protein immunotherapy	IgE-mediated food allergy	Subcutaneous, intranasal and oral	Immune deviation from Th2 to Th1 (?)	Appears safe
DNA immunization	IgE-mediated food allergy	Subcutaneous and oral	(Subcutaneous) Immune deviation from Th2 to Th1, (Oral) increase levels of allergen specific secretory IgA in gut, and increase systemic IgG	Unknown long-term
Immunostimulatory sequences (ISS)	IgE-mediated food allergy	Subcutaneous	Immune deviation from Th2 to Th1	Appears safe
Anti-IgE therapy	IgE-mediated food allergy	Subcutaneous	Depletes IgE, blocks IgE from binding to high affinity IgE-receptor (FcεRI), down-regulates IgE receptor production	Appears safe – anaphylaxis and malignancy noted but not increased

*Most risk assessment performed in animal studies but some preliminary studies performed in humans.

so many side-effects of treatment that, practically, it would be impossible to perform on a routine basis.

As traditional immunotherapy has been largely impractical for the treatment of most food allergies, several novel therapies are now being explored (Table 1).

Novel therapies

Techniques under current investigation for the treatment of food allergy in both animal models and humans include: peptide immunotherapy, Traditional Chinese Medicine, mutated protein immunotherapy, allergen DNA immunization, vaccination with immunostimulatory DNA sequences and anti-immunoglobulin E (Anti-IgE) therapy.

Peptide immunotherapy

Peptide immunotherapy utilizes peptide fragments containing T-cell reactive epitopes rather than complete protein molecules. Theoretically, these peptide fragments are unable to cross-link IgE molecules required to activate mast cells, but do appear to render T-cells unresponsive to subsequent allergen exposure [10]. In one study utilizing peptide immunotherapy, the investigators injected cat-allergic patients with T-cell reactive peptide fragments containing dominant cat allergen epitopes [11]. Patients tolerated the injections with few, mild adverse reactions. The investigators demonstrated that cat-allergic patients treated with the peptide fragments had statistically significant improvement in nasal, lung and total symptom scores when compared with placebo-treated subjects after exposure to cats [11]. A similarly related approach that has involved larger numbers of peptides from cat has been shown to be effective [12]. Cat-allergic patients treated with intradermal cat peptides developed a significant immune response, as well as clinical improvement in their symptoms. Another preliminary study demonstrated that pepsin-digested peanut allergen containing T-cell epitopes but no IgE-binding epitopes induced interferon-gamma (IFN- γ), a T-helper type 1 (Th1) cytokine, in a concentration-dependent manner [13]. Most recently, T-cell epitopes of the major peanut allergen Ara h 2 were mapped, laying down the groundwork for designing peptides that could be used in future in-vivo studies [14*]. While peptide immunotherapy for food allergy has not yet reached clinical trials, studies utilizing the peptides of the peanut allergens are encouraging and suggest the potential role for peptide immunotherapy in the future therapy of food allergy.

Traditional Chinese Medicine

Herbal remedies have been used in Asia for centuries for the treatment of allergic diseases [15,16]. They have a favorable safety profile and the advantage of a low cost. Recent studies have utilized Traditional Chinese

Medicine in a mouse model of peanut allergy [16,17^{••}]. A recent study was performed to test whether FAHF-2, an improved herbal formula, from which two herbs, *Zhi Fu Zi* (Radix Lateralis Aconiti Carmichaeli Praeparata) and *Xi Xin* (Herba Asari), were eliminated, is equally effective to FAHF-1 (used in the original studies) and, if so, whether protection persists after therapy is discontinued. After challenges, all sham-treated mice developed severe anaphylactic signs, significant decrease in rectal temperatures, significantly increased plasma histamine levels and marked vascular leakage. In contrast, no sign of anaphylactic reactions, decrease in rectal temperatures or elevation of plasma histamine levels was observed in FAHF-2-treated mice in five separate experiments. IgE levels were significantly reduced by the herbal formula (FAHF-2) treatment and remained significantly lower as long as 5 weeks after therapy. Splenocytes from FAHF-2-treated mice showed significantly reduced interleukin-4 (IL-4), IL-5 and IL-13, and enhanced IFN- γ production to recall peanut stimulation *in vitro*.

Mutated protein immunotherapy

With greater understanding of the allergic mechanism and better characterization of allergens, we and our collaborators [18,19] are developing techniques that appear to be both well tolerated and effective in the treatment of food allergy. This type of immunotherapy can be achieved through modification of the primary amino acid sequences of IgE-binding allergenic epitopes of the major allergens present in foods. Specific IgE binding to the food allergens occurs to the linear amino acid sequence compared with the IgE binding to inhaled allergens that bind to typically conformational epitopes [19]. By altering the primary amino acid sequence of the IgE epitopes, researchers have been able to substantially alter IgE antibody binding with the major peanut allergens as well as shrimp allergens, ranging from reduced binding to complete abolition of binding. Such mutations were introduced into the cDNA sequences of the major peanut allergens, Ara h 1, Ara h 2 and Ara h 3, which were then successfully expressed as less allergenic recombinant proteins [20,21]. Mutating the IgE-binding sites did not alter the T-cell epitopes, however. Patients with peanut hypersensitivity had dramatically reduced peanut-specific IgE binding to the mutated peanut protein when compared with the wild-type peanut protein. In animal studies with peanut-allergic mice, the mutated protein significantly reduced the amount of peanut-specific IgE antibody produced by the peanut-allergic animal, as well as reduced their clinical symptoms on peanut challenge [19,22]. The treated animals had a reduction in Th2 cytokines over the course of treatment, with data suggesting an increase in T-regulatory cells producing IL-10. There has also been demonstrated that the use of an adjuvant with a mutated allergen may

increase the likelihood of obtaining the desired immunologic effect and clinical protection [23,24^{••}].

Designing molecules that have reduced or abolished IgE binding, while preserving their ability to stimulate T-cells, should result in the availability of well tolerated and effective therapeutics for the treatment of food allergy. Furthermore, alteration of such molecules in foods theoretically could substantially reduce the incidence of food-induced anaphylactic reactions in such sensitized patients. This approach currently is very unlikely, however, because of the large numbers of allergens in each food.

Homologous protein immunotherapy

Like peanut, soybean belongs to the legume family. This taxonomic kinship is also reflected at the molecular level, as their respective seed storage proteins share significant amino acid sequence and three-dimensional structure homologies. The soybean counterparts of the three major peanut allergens, Ara h 1, Ara h 2 and Ara h 3, are the β -conglycinin, 2S albumin and glycinin proteins, respectively. These soybean proteins can be viewed as natural mutants of the peanut allergens and used as desensitizing agents in allergen-specific immunotherapy. This innovative concept was tested in a model of peanut-allergic mice [25[•]]. After peanut challenge, peanut-allergic mice which received soybean immunotherapy were equally protected as the ones which underwent peanut immunotherapy and their clinical symptoms were significantly reduced compared with the placebo-treated mice. Levels of peanut-specific IgG1 were significantly lowered after soybean treatment compared with peanut treatment. The cellular response to peanut was also down-regulated in the soybean-treated group, as demonstrated by diminished lymphoproliferative responses and immunodeviation of the remaining T-cell reactivity toward a more Th1/0-like response associated with the production of higher amounts of peanut-specific IFN- γ and tumor necrosis factor- α (TNF- α). A closer look at the amino acid sequence homologies between Ara h 2 and the soy 2S albumin revealed that most of the amino acid discrepancies were located in regions corresponding to the immunodominant IgE binding epitopes of Ara h 2, whereas regions corresponding to T-cell epitopes were more conserved. This related species homologue naturally harbors features that are sought when engineering intra-specific mutated allergens for immunotherapy.

If soybean immunotherapy can be used in patients allergic to peanuts and is effective, the treatment would provide an immediate and better tolerated therapeutic option for patients with peanut hypersensitivity.

DNA immunization

Another novel approach to the treatment of food allergy currently under investigation is DNA immunization

[26,27]. DNA immunization employs the subcutaneous injection of a plasmid DNA (pDNA) vector encoding a specific allergenic protein. The pDNA sequence is taken up by antigen presenting cells (APCs). Once inside the cell, the DNA encoding allergen is transcribed and translated. The allergen is then presumably presented on the surface of the APCs in the context of the major histocompatibility complex (MHC) to T-cells. This endogenously produced allergenic protein or protein fragment induces a Th1 phenotypic response with up-regulation of IFN- γ , an increase in IgG2a and suppression of allergen-specific IgE production [28,29]. Oral delivery of DNA immunizations has also been described. It has been utilized as an immunoprophylactic strategy to modulate peanut antigen-induced anaphylaxis [29]. In this model, the oral delivery of DNA complexed to chitosan, a biocompatible polysaccharide, also favored a Th1 response and suppressed the Th2 allergic immune response.

Immunization with immunostimulatory sequences

Another DNA immunization technique under investigation is immunization with pDNA conjugated to immunostimulatory sequences (ISS). These ISS contain unmethylated cytosine and guanine dinucleotide repeat motifs. These CpG motifs stimulate APCs and natural killer cells to secrete IFN- γ and IL-12 – cytokines that promote immune deviation toward the Th1 phenotype and away from the allergic Th2 phenotype [28]. These ISS stimulate immune deviation to the Th1 phenotype when administered in several ways. They can be administered with DNA encoding the allergen (DNA immunization) [30], given alone [31] or conjugated with allergen. Although the majority of these DNA immunization techniques have been studied in the mouse model, a recent study [32] describes enhanced immune deviation to the Th1 phenotype and reduced allergenicity after injection immunotherapy with the major ragweed allergen, Amb a 1, conjugated to ISS in mice and rabbits, as well as in primates. It is certain that studies with ISS conjugation to one or some of the peanut allergens will begin in the next few years.

Anti-IgE immunotherapy

In general, the immune response to allergen immunotherapy is allergen-specific, making treatment of multiple allergies complex and expensive. Often, patients are allergic to more than one allergen. Ideally, one would prefer to utilize a single therapy to combat the entire allergic mechanism – one therapeutic option that would be effective for multiple inhalant allergies as well as food allergies. One such therapy, already in clinical trials, involves the use of anti-IgE antibodies [33]. Immunoglobulin E (IgE) exists freely circulating or attached to mast cells and basophils. When two mast cell-bound IgE molecules are cross-linked by antigen, the cell is

activated and vasoactive mediators are released. Anti-IgE, a humanized mouse monoclonal IgG antibody, directed against the human IgE molecule, binds to freely circulating IgE and not to mast cell or basophil-bound IgE. Once circulating IgE is bound by anti-IgE, it is unable to bind to its specific high-affinity receptor (Fc ϵ RI) on mast cells and basophils. These antigen-antibody complexes are then cleared from the circulation by the reticuloendothelial system without activation of complement. Several clinical trials involving patients with allergic rhinitis [34] and allergic asthma [35] have been completed. Statistically significant reductions in medication use, allergic symptoms and airways hyperactivity have been described following anti-IgE treatment. Reductions in total serum IgE levels to less than 1% of pretreatment levels were noted in addition to down-regulation of the high-affinity IgE-receptor (Fc ϵ RI) [36].

A recent study of 84 patients with peanut hypersensitivity treated with anti-IgE has been completed [33]. A significant number of patients receiving the highest dose of anti-IgE monthly for 4 months had a significant decrease in their clinical symptoms following peanut challenge after treatment. Patients received 150, 300 or 450 mg of anti-IgE monthly for 4 months. After treatment, the subjects had a peanut challenge. At baseline, they tolerated about half a peanut and on the highest treatment dose, they were able to tolerate almost nine peanuts. One problem with the study, though, is that 25% of the subjects, even in the high-dose group, had no change of their tolerance to peanuts after treatment.

Although anti-IgE therapy is expensive and requires frequent administration to maintain the IgE-deficient state, it could theoretically be used quite effectively in conjunction with other therapeutic modalities. For example, pretreatment with anti-IgE could potentially prevent the systemic reactions experienced with peanut immunotherapy [8] while achieving the beneficial effects of desensitization. This promising technique is currently under investigation in patients who have food allergy.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 582).

- 1 Noon L, Cantab B. Prophylactic inoculation against hay fever. *Lancet* 1911; 177:1572–1573.
- 2 Freeman J. 'Rush' inoculation, with special reference to hay fever. *Lancet* 1930; 215:744–747.
- 3 Asero R. Effects of birch pollen-specific immunotherapy on apple allergy in birch pollen-hypersensitive patients. *Clin Exp Allergy* 1998; 28:1368–1373.
- 4 Asero R. Fennel, cucumber, and melon allergy successfully treated with pollen-specific injection immunotherapy. *Ann Allergy Asthma Immunol* 2000; 84:460–462.

- 5 Bolhaar ST, Tiemessen MM, Zuidmeer L, *et al.* Efficacy of birch-pollen immunotherapy on cross-reactive food allergy confirmed by skin tests and double-blind food challenges. *Clin Exp Allergy* 2004; 34:761–769.
- 6 Bucher X, Pichler WJ, Dahinden CA, Helbling A. Effect of tree pollen specific, subcutaneous immunotherapy on the oral allergy syndrome to apple and hazelnut. *Allergy* 2004; 59:1272–1276.
- 7 Burks AW. Classic specific immunotherapy and new perspectives in specific immunotherapy for food allergy. *Allergy* 2003; 67:121–124.
- 8 Oppenheimer JJ, Nelson HS, Bock SA, *et al.* Treatment of peanut allergy with rush immunotherapy. *J Allergy Clin Immunol* 1992; 90:256–262.
- 9 Nelson HS, Lahr J, Rule R, *et al.* Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. *J Allergy Clin Immunol* 1997; 99:744–751.
- 10 Briner TJ, Kuo MC, Keating KM, *et al.* Peripheral T-cell tolerance induced in naive and primed mice by subcutaneous injection of peptides from the major cat allergen Fel d 1. *Proc Natl Acad Sci U S A* 1993; 90:7608–7612.
- 11 Norman PS, Ohman JL Jr, Long AA, *et al.* Treatment of cat allergy with T-cell reactive peptides. *Am J Respir Crit Care Med* 1996; 154:1623–1628.
- 12 Oldfield WL, Larche M, Kay AB. Effect of T-cell peptides derived from Fel d 1 on allergic reactions and cytokine production in patients sensitive to cats: A randomised controlled trial. *Lancet* 2002; 360:47–53.
- 13 Hong SJ, Michael JG, Fehring A, Leung DY. Pepsin-digested peanut contains T-cell epitopes but no IgE epitopes. *J Allergy Clin Immunol* 1999; 104:473–478.
- 14 Glaspole IN, de Leon MP, Rolland JM, O'Hehir RE. Characterization of the T-cell epitopes of a major peanut allergen, Ara h 2. *Allergy* 2005; 60:35–40. An interesting study that will help in the development of a peanut allergy vaccine.
- 15 Li XM, Zhang TF, Huang CK, *et al.* Food Allergy Herbal Formula-1 (FAHF-1) blocks peanut-induced anaphylaxis in a murine model. *J Allergy Clin Immunol* 2001; 108:639–646.
- 16 Li XM, Sampson HA. Novel approaches for the treatment of food allergy. *Curr Opin Allergy Clin Immunol* 2002; 2:273–278.
- 17 Srivastava KD, Kattan JD, Zou ZM, *et al.* The Chinese herbal medicine formula FAHF-2 completely blocks anaphylactic reactions in a murine model of peanut allergy. *J Allergy Clin Immunol* 2005; 115:171–178.
- A fascinating study that will help in understanding the mechanism of peanut allergy.
- 18 Burks W, Lehrer SB, Bannon GA. New approaches for treatment of peanut allergy: Chances for a cure. *Clin Rev Allergy Immunol* 2004; 27:191–196.
- 19 Li XM, Srivastava K, Grishin A, *et al.* Persistent protective effect of heat-killed *Escherichia coli* producing 'engineered,' recombinant peanut proteins in a murine model of peanut allergy. *J Allergy Clin Immunol* 2003; 112:159–167.
- 20 Stanley JS, Helm RM, Cockrell G, *et al.* Peanut hypersensitivity: IgE binding characteristics of a recombinant Ara h I protein. *Adv Exp Med Biol* 1996; 409:213–216.
- 21 Stanley JS, King N, Burks AW, *et al.* Identification and mutational analysis of the immunodominant IgE binding epitopes of the major peanut allergen Ara h 2. *Arch Biochem Biophys* 1997; 342:244–253.
- 22 Li XM, Serebrisky D, Lee SY, *et al.* A murine model of peanut anaphylaxis: T- and B-cell responses to a major peanut allergen mimic human responses. *J Allergy Clin Immunol* 2000; 106:150–158.
- 23 Li XM, Srivastava K, Huleatt JW, *et al.* Engineered recombinant peanut protein and heat-killed *Listeria monocytogenes* coadministration protects against peanut-induced anaphylaxis in a murine model. *J Immunol* 2003; 170:3289–3295.
- 24 Frick OL, Teuber SS, Buchanan BB, *et al.* Allergen immunotherapy with heat-killed *Listeria monocytogenes* alleviates peanut and food-induced anaphylaxis in dogs. *Allergy* 2005; 60:243–250.
- An excellent study that will help in the future development of treatments for peanut allergy.
- 25 Pons L, Ponnappan U, Hall RA, *et al.* Soy immunotherapy for peanut-allergic mice: Modulation of the peanut-allergic response. *J Allergy Clin Immunol* 2004; 114:915–921.
- An interesting study that provides information that will help us learn more about the allergens necessary for treatment of peanut-allergy patients.
- 26 Slater JE, Colberg-Poley A. A DNA vaccine for allergen immunotherapy using the latex allergen Hev b 5. *Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankfurt A M* 1997; 91:230–235.
- 27 Spiegelberg HL, Orozco EM, Roman M, Raz E. DNA immunization: A novel approach to allergen-specific immunotherapy. *Allergy* 1997; 52:964–970.
- 28 Chu RS, Targoni OS, Krieg AM, *et al.* CpG oligodeoxynucleotides act as adjuvants that switch on T helper 1 (Th1) immunity. *J Exp Med* 1997; 186:1623–1631.
- 29 Roy K, Mao HQ, Huang SK, Leong KW. Oral gene delivery with chitosan–DNA nanoparticles generates immunologic protection in a murine model of peanut allergy. *Nat Med* 1999; 5:387–391.
- 30 Hsu CH, Chua KY, Tao MH, *et al.* Immunoprophylaxis of allergen-induced immunoglobulin E synthesis and airway hyperresponsiveness *in vivo* by genetic immunization. *Nat Med* 1996; 2:540–544.
- 31 Bohle B, Jahn-Schmid B, Maurer D, *et al.* Oligodeoxynucleotides containing CpG motifs induce IL-12, IL-18 and IFN-gamma production in cells from allergic individuals and inhibit IgE synthesis *in vitro*. *Eur J Immunol* 1999; 29:2344–2353.
- 32 Tighe H, Takabayashi K, Schwartz D, *et al.* Conjugation of immunostimulatory DNA to the short ragweed allergen amb a 1 enhances its immunogenicity and reduces its allergenicity. *J Allergy Clin Immunol* 2000; 106:124–134.
- 33 Leung DY, Sampson HA, Yunginger JW, *et al.* Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med* 2003; 348:986–993.
- 34 Nayak A, Casale T, Miller SD, *et al.* Tolerability of retreatment with omalizumab, a recombinant humanized monoclonal anti-IgE antibody, during a second ragweed pollen season in patients with seasonal allergic rhinitis. *Allergy Asthma Proc* 2003; 24:323–329.
- 35 Milgrom H, Fick RB Jr, Su JQ, *et al.* Treatment of allergic asthma with monoclonal anti-IgE antibody. *rhuMab-E25 Study Group. N Engl J Med* 1999; 341:1966–1973.
- 36 Saini SS, MacGlashan DW Jr, Sterbinsky SA, *et al.* Down-regulation of human basophil IgE and FC epsilon RI alpha surface densities and mediator release by anti-IgE-infusions is reversible *in vitro* and *in vivo*. *J Immunol* 1999; 162:5624–5630.