

Beyond allergen avoidance: update on developing therapies for peanut allergy

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Purpose of review

Food allergy has emerged as a significant health problem. Peanut allergy is a major cause of food-induced fatal and near fatal anaphylactic reactions, and the incidence in children is increasing. Attempts to manage peanut allergy by strict avoidance are often unsuccessful. The purpose of this review is to highlight the most promising novel approaches for treating peanut allergy beyond allergen avoidance.

Recent findings

In the past 5 years much effort has been devoted to developing a treatment for peanut allergy. A recent clinical trial showed that monthly injections of humanized recombinant anti-IgE antibodies increased the threshold for allergic responses of peanut-sensitive individuals, at least to small amounts of peanut protein. However, this treatment cannot cure peanut allergy, and continuous monthly injections are necessary to maintain protection. Developing new therapies for the treatment of peanut allergy is essential. In reviewing publications between 2003 and 2005, several novel therapeutic approaches, tested in the murine model of peanut anaphylaxis appeared promising. Immunotherapy with engineered recombinant peanut protein and bacterial adjuvant significantly protected peanut allergic mice from anaphylaxis. It was also found that a Chinese herbal medicine formula called Food Allergy Herbal Formula-2 completely blocked anaphylaxis up to 5 weeks following therapy. These potent therapeutic effects are associated with immunoregulation of Th1 and Th2 responses.

Summary

Although there is no effective and safe therapy for food allergy, many novel approaches are under investigation. Some of these approaches may provide allergists with effective treatments in the near future.

Keywords

Chinese herbal medicine, engineered recombinant peanut protein and bacterial adjuvant, food allergy, novel immunotherapy

Abbreviations

FAHF	Food Allergy Herbal Formula
HKE	heat-killed <i>Escherichia coli</i>
HKLM	heat-killed <i>Listeria monocytogenes</i>
MP123	mixture of equal proportions of mAra h1, mAra h2 and mAra h3
PNA	peanut allergy

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Introduction

Food allergy affects up to 6% of children under 4 years of age and about 2% of the US population beyond the first decade of life [1]. It is the leading cause of anaphylaxis treated in hospital emergency departments in the US. Peanut and tree nut allergies account for approximately 80% of fatal and near-fatal anaphylactic reactions [2,3]. The prevalence of childhood peanut allergy (PNA) doubled between 1997 and 2002 [4], and although most food allergies are outgrown, PNA is usually life long [5]. PNA has a severe negative impact on the quality of life of affected children and their families [6]. At present, the only way to manage PNA and other food allergies is strict avoidance, but because peanut is a 'hidden' ingredient in a number of processed foods, accidental ingestions, sometimes resulting in fatal and near-fatal reactions, are common. It has been estimated that about 50% of peanut-allergic patients will experience an accidental reaction to peanuts over a 2-year period [4]. This indicates that 'avoidance treatment' alone is an unrealistic therapeutic strategy for patients with PNA. Recent efforts to develop treatments for PNA will be the focus of this review.

A recent clinical trial showed that monthly injections of humanized recombinant anti-IgE antibodies increased the threshold for allergic responses of peanut-sensitive individuals, at least to small amounts of peanut protein [7]. However, this treatment is very expensive, and continued monthly injections are necessary to maintain protection. Furthermore, there is some concern regarding possibly increased cancer prevalence associated with anti-IgE therapy [8]. Developing new therapies for the treatment of PNA is essential.

Numerous studies have shown that Th2 cytokines are central to the pathogenesis of allergic disorders [9], and a Th2-skewed response has been found in food allergy. Peanut-specific Th2 clones have also been generated

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from patients with PNA [10,11]. There is evidence that tolerance to food antigens, induced via the gut, is determined by an IFN- γ involved immune mechanism [12,13] and one recent study suggested that the peanut-allergic status is characterized by a Th2 response whereas Th1-skewed responses underlie oral tolerance [14]. According to the hygiene hypotheses, the increasing incidence of allergy in Westernized societies over the last decades [15] may be explained, to some extent, by a reduced microbial load early in infancy, which results in too little Th1 cell activity, and therefore insufficient IFN- γ to optimally cross-regulate Th2 responses [12,16–18]. Recent advances in the understanding of the immunological mechanisms of food allergy, in the characterization of food allergens [19], and in novel vaccination approaches enable the development of new immunotherapeutic approaches to the treatment of food allergy. The murine model of peanut anaphylaxis, which physiologically and immunologically mimics PNA in humans, has been used to explore novel approaches for PNA [20–23].

Novel approaches for peanut allergy

As reviewed two years ago, several novel immunotherapeutic approaches for PNA were investigated, including plasmid DNA-based immunotherapy, immunostimulatory-oligodeoxynucleotide (ISS-ODN)-based immunotherapy, mutated protein immunotherapy, peptide immunotherapy, bacterial therapy, anti-IgE therapy, cytokine therapy, and herbal medicine [24]. Since then, several new investigations into novel immunotherapeutic approaches for PNA have been published. It has been reported that soy protein immunotherapy of peanut-allergic mice reduced symptom scores, increased body temperatures, reduced serum IgG1, and increased IFN- γ and tumor necrosis factor (TNF)- α levels [25[•]]. However, intraperitoneal soy immunotherapy is not clinically applicable. In addition, extrapolating the results of that study to peanut-sensitized humans may be problematic because many patients allergic to peanut already show an immune response to soy [25[•]]. It was also reported that subcutaneous vaccination with peanut allergen and heat-killed *Listeria monocytogenes* (HKLM) increased the threshold for peanut allergen-induced skin reactions and symptoms in peanut-allergic dogs [26[•]]. However, there are potential safety concerns about applying this approach to humans. Because therapeutic strategies for food allergies must be safe, relatively inexpensive, and easily administered [27[•]], after considering the potency and persistence of our previous methods, several approaches have been abandoned, including plasmid DNA encoding wild type peanut protein, because of the risk of anaphylaxis [28]. This approach was refined by generating plasmid DNA constructs encoding mutated peanut proteins in order to increase the safety profiles [29]. New approaches to the murine model of PNA were also investigated, such as CpG oligodeoxynucleotide

(CpG ODN) administration [30], coadministration of modified peanut proteins (m Ara h1, 2 and 3) and HKLM (m Ara h1–3 + HKLM) [31], and a mixture of heat-killed *Escherichia coli* producing m Ara h1, 2, and 3 (HKE-MP123) [32]. The Food Allergy Herbal Formula-2 (FAHF-2) [33^{••}], which is an improved version of the original formula FAHF-1, was also generated. A brief summary of each approach is presented in Table 1. The following section describes what appeared to be the most clinically relevant studies.

Engineered recombinant peanut protein and heat-killed *L. monocytogenes* coadministration protects against peanut-induced anaphylaxis in a murine model

In traditional immunotherapy using antigen extracts, the benefit-to-risk ratio for injections of peanut extract is unacceptable [34]. To investigate safe and effective immunotherapeutic approaches for treating PNA, investigators generated engineered (mutated) peanut proteins, modified (m)Ara h1, mAra h2 and mAra h3 (mAra-h123), in which IgE binding epitopes were altered by a critical amino acid within the IgE binding site (epitope) to eliminate or drastically reduce IgE binding to the protein [35,36], thereby reducing the risk of eliciting allergic reactions. It was found that, compared with wild type peanut allergen protein, modified peanut allergen proteins showed some protection in peanut-sensitized mice following intranasal administration. However, desensitization required frequent administrations, and subcutaneous desensitization – the standard route for immunotherapy – produced little protection (X.M. Li, K. Srivastava, H. Sampson, unpublished data). These results suggested that engineered peanut protein immunization alone is probably not adequate for treating PNA.

HKLM, a potent activator of the innate immune system, has been employed as an adjuvant in immunotherapeutic desensitization of mice. Yeung *et al.* [37] showed that coadministration of HKLM and keyhole limpet hemocyanin (KLH) to KLH-sensitized mice reduced Th2 cytokines and IgE production, and increased IFN- γ production. Hansen *et al.* [38] showed that coadministration of HKLM and ovalbumin prevented and reversed established airway hyperreactivity in a murine model of allergic asthma. The findings that HKLM is a strong Th1 adjuvant suggested that HKLM may also enhance the efficacy of modified peanut protein-based immunotherapy.

A previous study [31] investigated the effect of coadministration of modified peanut proteins (mAra h1, 2 and 3) and HKLM as an adjuvant (mAra h1–3 + HKLM) on a murine model of peanut hypersensitivity, and found that this treatment reduced the number of mice with anaphylaxis upon peanut challenge by approximately 70%. In

Table 1. Investigation of novel therapeutic approaches for peanut allergy in animal models

Therapy	Form	Effect	Comment
Plasmid DNA	Encoding wAra h2 (pAraH2, i.m.) Encoding mAra h2* (pmAra h2, i.n. or pr)	Prophylactic protocol: no effect on IgE, increase in IgG2a, prevents Ara h2-induced anaphylaxis in AKR mice, but induces anaphylaxis in C3H mice Therapeutic protocol in C3H/J mice: reduced IgE in sensitized C3H/J mice, partially protected against peanut-induced anaphylaxis, reduced IL-4 and increased IFN- γ	Serious concerns regarding safety No anaphylactic reaction was observed during treatment
ISS-ODN	ISS-conjugated-Ara h2 (i.d.) CpG ODN* (i.n.)	Prophylactic protocol in C3H/J mice: partially prevented Ara h2-induced anaphylaxis in C3H/J mice, no significant reduction of IgE, increased Th1 cytokine levels Therapeutic protocol in C3H/J mice: slight reduction of peanut-specific IgE levels, increased IgG2a, completely protected against anaphylactic reactions in response to peanut challenge	Difficult to prepare material; desensitization of established peanut allergy has not been established Less effective on peanut-specific IgE, effect on cytokine profiles has not been defined
Peptides	20-mers Ara h 2 peptide mixture (s.c.)	Therapeutic protocol in C3H/J mice: reduced Ara h 2-specific IgE, reduced anaphylaxis scores, and increased IFN- γ production by spleen cells	Very expensive
Mutated protein	mAra h2 or a mixture of mAra h1, 2 and 3 (i.n. or s.c.)	Therapeutic protocol in C3H/J mice: reduced IgE, and severity of anaphylactic reactions, reduced IL-4, did not increase IFN- γ	Frequent i.n. administrations required; s.c. desensitization, the standard route for immunotherapy, produced little protection
Soy*	Crude soybean extract (i.p.)	Therapeutic protocol in C3H/J mice: reduced peanut-specific IgG1, reduced anaphylactic symptom scores, increased IFN- γ and TNF- α	i.p. sensitization and i.p. soy immunotherapy not clinically applicable
Bacterial	mAra h1-3 + HKLM* (s.c.) Peanut antigen + HKLM* (s.c.) HKE-MP123* (pr)	Therapeutic protocol in C3H/J mice: reduced peanut-specific IgE, partially protected from anaphylaxis, reduced IL-4, IL-5, IL-13 production and increased IFN- γ production by splenocytes Therapeutic protocol in dogs: increased the threshold for peanut allergen-induced skin reactions and symptoms in peanut-allergic dogs Therapeutic protocol in C3H/J mice: reduced peanut-specific IgE, partially protected from anaphylaxis, reduced IL-4, IL-5, IL-13 and IL-10 production by splenocytes and increased IFN- γ and TGF- β by splenocytes. Therapeutic effect lasted at least 10 weeks	Safety remains to be determined. Long-lasting therapeutic effect has not been established Potential risk of using peanut protein, no placebo controls, no effect on cytokine profiles reported Less concern regarding activating mast cells, little concern about safety of such vaccine administration, relatively long-lasting effect
Chinese herbal medicine	FAHF-1 (oral) FAHF-2* (oral), an improved herbal formula from which two potentially toxic herbs in FAHF-1 were eliminated	Therapeutic protocol in C3H/J mice: prevented systemic anaphylactic symptoms and histamine release, peanut-specific serum IgE, and Th2 cytokine secretion, and had no toxic effects on liver or kidney functions Therapeutic protocol in C3H/J mice: reduced peanut specific IgE, completely blocked anaphylactic reactions, reduced IL-4, IL-5 and IL-13, and enhanced IFN- γ production. Therapeutic effect lasted at least 6 months following therapy	Oral, generally safe and well tolerated, most potent effect on peanut allergy. Long-term protection of FAHF-2, large safety margin, less costly, may be effective for other food allergies, planning clinical trials of FAHF-2 under the FDA botanical drug mechanism

W, wild type; m, modified; i.m., intramuscular; i.n., intranasal; pr, per rectal; ISS-ODN, immunostimulatory-oligodeoxynucleotide; i.d., intradermal; CpG ODN, CpG oligodeoxynucleotide; s.c., subcutaneous; i.p., intraperitoneal; TNF, tumor necrosis factor; mAra h1-3 + HKLM, coadministration of modified peanut proteins (m Ara h1, 2 and 3) and heat-killed *Listeria monocytogenes*; HKE-MP123, heat-killed *Escherichia coli* producing mAra h1, 2 and 3; TGF, transforming growth factor; FAHF, Food Allergy Herbal Formula. An asterisk indicates new studies after the review by Li and Sampson [24].

accordance with these findings, body temperatures and peak expiratory flow value were significantly higher, and plasma histamine levels were significantly lower in mAra h1-3 + HKLM-treated mice than in sham-treated mice. Furthermore, IgE levels were significantly reduced and IgG2a levels were significantly increased in the mAra h1-3 + HKLM-treated group compared with the sham-treated group. In addition, IL-4, IL-5 and IL-13 production was significantly reduced whereas IFN- γ production was significantly increased in cultured lymphocytes from mAra h1-3 + HKLM-treated mice. Treatment with mAra h1-3 alone had significantly less effect on hypersensitivity reactions and histamine release, and no effect on IgE synthesis despite an increased number of treatments [31]. These results showed that immunotherapy with modified peanut protein and HKLM as adjuvant may be a potential approach for treating peanut hypersensitivity. Although modified peanut proteins reduce the concern regarding activation of mast cells during desensitization, the safety and tolerability of subcutaneous administration of HKLM remain to be determined.

Potency and persistency of heat-killed *E. coli* producing mAra h1-3 effects on peanut hypersensitivity

Since engineered peanut proteins are generated in *E. coli*, which may serve as an adjuvant promoting a Th1 response, subsequent studies investigated the efficacy of a mixture of HKE producing mAra h1, 2, and 3 (HKE-MP123). We found that administering this mixture subcutaneously or rectally, but not intragastrically, significantly suppressed PNA (X.M. Li, K. Srivastava, H. Sampson, unpublished data). The subcutaneous route was abandoned because it induced skin inflammation and is unlikely to be acceptable for human use. Since the rectal mucosa is heavily colonized with *E. coli* and other organisms, the efficacy of rectal administration of HKE-MP123 was compared with a mixture of the same purified modified peanut allergenic proteins alone (MP 123). It was found that HKE-MP123 treatment significantly reduced anaphylactic symptom scores, plasma histamine levels and serum IgE levels, and increased IgG2a levels. These effects were accompanied by increased Th1 and decreased Th2 cytokine production. MP-123 alone showed no significant effects (X.M. Li, K. Srivastava, H. Sampson, unpublished data). Next, the persistence of per rectal HKE-MP123 effects was evaluated and it was found that protection lasted for at least 10 weeks following treatment. IgG2a levels were significantly increased whereas IgE levels were significantly reduced [32]. Furthermore, IL-4, IL-5, IL-13 and IL-10 production by splenocytes from HKE-MP123-treated mice was significantly reduced whereas IFN- γ and transforming growth factor- β production was significantly increased [32]. These results demonstrated that treatment with

rectally administered HKE-MP123 can induce long-term 'downregulation' of peanut hypersensitivity.

In addition to HKE's adjuvant activity, and the fact that the mutated recombinant proteins in HKE are of less concern than native peanut proteins when it comes to the risk of eliciting an allergic response, HKE-MP123 treatment has several other benefits as a novel immunotherapeutic approach for PNA treatment. First, because the engineered peanut proteins are generated in *E. coli* using HKE, producing engineered peanut protein does not require purifying the recombinant peanut proteins and is therefore less time consuming and costly. Secondly, HKE cells are still intact, thereby preventing the peanut proteins from activating mast cells, resulting in an additional level of safety. Lastly, because HKE-MP123 is administered into an environment replete with *E. coli* and other bacteria, there is less concern about safety of such vaccine administration. Therefore, this approach appears to be superior to coadministration of HKLM and purified engineered peanut proteins. Although rigorous investigation is required to confirm the safety of this approach, no signs of anaphylactic reactions were found during the desensitization course, or any local inflammatory reactions. These studies suggest that HKE-MP123 may be a potential therapeutic approach for PNA.

Chinese herbal medicine therapy for food allergy

Traditional Chinese medicine has been used in China and other Asian countries for centuries and has shown some potential in treating allergic diseases, including asthma [39,40]. A herbal formula, FAHF-1, was previously reported to block systemic anaphylactic signs and reduce mast cell degranulation and histamine release, peanut-specific serum IgE level and Th2 cytokine secretion in a murine model of PNA [41]. FAHF-1 is nontoxic in an animal model. These results suggested that herbal medicines may have potential in the development of novel therapies for PNA. To increase the ease of standardization of this herbal product and improve its safety profile, over the past 2 years attempts have been made to simplify FAHF-1. Two herbs – *Zhi Fu Zi* (Radix Lateralis Aconiti Carmichaeli Praeparata) and *Xi Xin* (Herba Asari) – have been eliminated because they are not likely to be the principal herbs based on the traditional Chinese medicine formulation system [42] and may be toxic if incorrectly processed or overdosed [43–45]. This refined formula was called FAHF-2 [33•]. In a preliminary study [41], the efficacy of FAHF-2 was compared with FAHF-1 on peanut anaphylaxis using the original protocol in which mice were challenged with peanut immediately after completing treatment. It was found that FAHF-2 also completely blocked anaphylaxis following peanut challenge. The study was then extended so that peanut-allergic mice were challenged

1, 3, or 5 weeks following therapy in a series of five experiments. It was found that FAHF-2-treated mice were completely protected from anaphylaxis following challenge for up to 5 weeks following therapy, and that reduced IgE levels remained significantly lower at 5 weeks [33^{••}]. Complete protection was confirmed using several well established parameters, including anaphylactic symptom scores, decreased core body temperatures, elevated plasma histamine levels [41] and vascular leakage [46]. The findings were reproduced in a series of five experiments at different challenge times following therapy [33^{••}], demonstrating a potent and a consistent effect of FAHF-2 therapy on PNA. This therapeutic effect was associated with immunoregulatory effects on Th1–Th2 responses [33^{••}]. Furthermore, this formula appears to have a large margin of safety. Mice fed 24 times the effective daily dose showed no signs of acute toxicity, no evidence of abnormal liver or kidney function, and no abnormal complete blood count or histology of major organs.

Since mice in the FAHF-2 treated group were still fully protected against peanut challenge 5 weeks following treatment, these studies were extended and it was found that FAHF-2 prevented anaphylactic reactions following multiple re-challenges for at least 6 months (~1/4 the life expectancy of mice) (K. Srivastava, C.F. Qu, X.M. Li, in preparation). The potent and long-lasting protection against PNA by FAHF-2 has not been established by any other therapeutic regime. If the same results are found in humans, FAHF-2 may provide a highly effective treatment for individuals with PNA.

Further tests were carried out on individual herbs contained in FAHF-2 and several more simplified formulas derived from FAHF-2. Interestingly, while FAHF-2 provides full spectrum protection against PNA, none of the individual herbs or further reduced formulas was as effective on PNA (J. Kattan, K. Srivastava, X.M. Li, in preparation). These results indicate that FAHF-2 formulas, although more complicated, appear to have advantages over individual herbs or more simple formulas. Given the efficacy and safety of FAHF-2 in our animal model of peanut anaphylaxis, phase I and II clinical trials with FAHF-2 are planned under the FDA botanical drug approval mechanism.

Conclusion

Although there is no effective and safe therapy for food allergy, many novel approaches are under investigation. Some of these approaches may provide allergists with effective treatments in the near future.

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