Recent advances in the diagnosis and therapy of peanut allergy

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Peanut allergy is a life-threatening, IgE-mediated allergic disease. The prevalence of peanut allergy in school-aged children is reported to be in excess of 1% and continues to rise, representing a major public health concern. Peanut allergy is diagnosed on the basis of a relevant clinical history combined with results of skin-prick testing and/or peanut-specific IgE levels. A double-blind placebo-controlled oral food challenge is the gold standard for diagnosis. Currently, there is no approved treatment or disease-modifying therapy for peanut allergy. This review discusses recent advances in molecular diagnostic techniques for peanut allergy and highlights advances in peanut allergy therapeutics, discussing allergen-specific and allergen-nonspecific treatments that are currently in Phase I/II clinical trials.

Keywords: allergen-nonspecific • allergen-specific • allergy • component resolved • diagnosis • diagnostics • IgE-mediated • immunotherapy • peanut • treatment

Peanut allergy occurs is unclear. Several studies have focused on the role of maternal consumption of allergen during pregnancy or lactation; however, interventional studies have failed to demonstrate any benefit of dietary elimination [25,26]. It has been hypothesized that peanut sensitization may occur as a consequence of environmental exposure through cutaneous or inhalational routes rather than from maternal or infant allergen [23]. While peanut allergy appears to have strong heritability, its genetic basis is unknown [27]. Given that loss-of-function mutations within the filaggrin gene are associated with atopic diseases such as atopic dermatitis, it is felt that filaggrin may also be a candidate gene in the etiology of peanut allergy [27,28]. In the past few years, much effort has been dedicated to the development of more sensitive and accurate diagnostic tools for the diagnosis of peanut allergy and this review discusses some of those advances (Box 1). There is a strong recognition of the unmet need to develop effective treatments for peanut allergy, and much progress has been made in the development of novel therapies, which are showing promise. While there is currently no approved treatment available for peanut allergy beyond allergen avoidance, it is probable that the current work in the field will soon lead to the development of a disease-modifying therapy for peanut allergy.
Advances in peanut allergy diagnostics

Allergen component-resolved diagnostics has become the focus of attention, because it offers the potential to become a more accurate diagnostic tool than those already established. Instead of crude allergen extracts, this method utilizes purified allergen proteins, which are produced from natural allergen sources or by recombinant expression of allergen-encoding cDNA [22]. Several studies have suggested that component-resolved diagnostics could improve the specificity of peanut-allergy testing. Koppelman et al. showed that Ara h 2 was the most important allergen in predicting clinical reactivity to peanut as 26 out of 32 peanut-allergic subjects in their cohort recognized it [31]. Nicolaou et al. demonstrated that Ara h 2 was the most important predictor of clinical peanut allergy, showing that Ara h 2-specific IgE levels >0.35 kU/l resulted in 100% sensitivity and 96.1% specificity in identifying subjects with peanut allergy, correctly identifying 97.5% of peanut-allergic subjects in their cohort [32]. Other studies also show that compared with whole peanut-specific IgE levels that are currently used for \textit{in vitro} testing, Ara h 2-specific IgE levels provide higher accuracy in diagnosing peanut allergy [33,34]. Currently the best method for diagnosis in an individual patient is the peanut-specific IgE; as other studies are completed, it will be interesting to see whether component testing replaces the crude allergen testing.

Several studies have shown that the pattern of binding to peanut proteins may vary according to the geographic location [35–39]. Other studies suggest that component testing can help in assessing the severity of an allergic reaction. Binding to Ara h 8, without binding to Ara h 1–3, has been shown to be associated with no reaction or mild reactions [40,41]. In addition, individuals who have isolated Ara h 8 sensitization typically have lower peanut-specific IgE and are sensitized to birch pollen [39–41]. Using either purified or recombinant peanut proteins, Peeters et al. [42], Palmer et al. [43] and Astier et al. [44] have published studies indicating increased potency of Ara h 2 [39]. However, it is important to point out that studies have not yet specifically correlated clinical severity with Ara h 2 IgE [39]. Hence, at this time, Ara h 2 cannot be used to predict the severity of a clinical reaction in peanut-allergic individuals.

Protein microarrays permit the simultaneous assessment of specific IgE to different peanut protein components. This technique requires small amounts of sera, which is an important consideration in children and may be a cost-efficient approach because it delivers results for multiple components simultaneously [32,45]. Microarray technology can potentially provide additional information, such as assessment of relative IgE antibody affinity [45,46] and the parallel determination of different antibody isotypes [45,47].

IgE-binding epitopes have recently been recognized as important factors in driving allergic reactions to peanut [32,45]. Partially digested and absorbed peanut protein may lead to IgE antibodies that recognize a greater number or a specific pattern of sequential epitopes [45]. This pattern may be indicative of clinical peanut allergy rather than asymptomatic sensitization [48] and studies have shown that greater IgE epitope diversity and/or higher affinity may be suggestive of the persistence and severity of peanut allergy [49,50].
In the future, combining component-resolved diagnostics, IgE epitope mapping and high-throughput microarray platforms may allow for an assay that will result in better diagnostic capability and help identify patients at risk for persistent allergy.

Several functional assays such as the basophil activation tests [51] and analysis of peanut-specific T-cell responses [52] are currently being studied. However, currently there is a lack of evidence demonstrating that these tests have diagnostic value in peanut allergy.

**Advances in treatment of peanut allergy: allergen-specific approaches**

The concept of approaching food allergy with strategies beyond allergen avoidance is certainly not a new one and dates back more than 100 years. Despite much effort through the years, there is currently no approved treatment for peanut allergy.

Although subcutaneous immunotherapy is used effectively and successfully to treat environmental allergies, this has not been a popular approach for food allergy. A few earlier studies explored the concept of subcutaneous peanut immunotherapy [53,54]. Although there was some evidence that injected peanut allergen could induce desensitization, the high rate of severe adverse reactions with subcutaneous peanut immunotherapy were considered unacceptable, and this approach was abandoned [54,55]. Thus began the pursuit for alternative approaches for treatment of peanut allergy.

**Peanut oral immunotherapy**

Oral immunotherapy (OIT) for peanut allergy in young children is one of the most studied research options because of promising results that have been seen with OIT for other foods [56–58]. During peanut OIT, doses of peanut allergen are mixed in a food vehicle and ingested by the subject in gradual incremental doses. Most OIT studies consist of an initial escalation phase that typically occurs in a closely supervised setting such as a research study center, followed by buildup and maintenance phases carried out at home.

When it comes to effective outcomes, there are two important concepts to keep in mind while reviewing OIT studies. The first is the concept of desensitization in which daily consumption of food allergen is required in order to maintain protection or a desensitized state. As a result, the threshold of the amount of protein needed to induce a clinical reaction is raised, but only as long as regular ingestion is continued. The next concept is that of clinical tolerance, which can be defined as the ability to ingest food protein without allergic symptoms in the absence of daily OIT, despite prolonged periods of avoidance of food protein [59,60]. While the optimal way to measure clinical tolerance is unknown, development of clinical tolerance in research studies is tested by interruption of OIT dosing for at least 4 weeks or longer followed by a supervised oral food challenge [59,61,62]. In large part, the results of the OIT studies to date are dependent on the dose and length of treatment.

In 2009, Jones et al. reported results of an open-label, multicenter uncontrolled trial of peanut OIT [63]. Even though these patients did not undergo an entry challenge, all subjects reacted at less than 50 mg of protein on the initial-day escalation indicating their clinical sensitivity. The study showed that 93% (27 out of 29) of subjects were desensitized, that is, they were able to successfully consume the entire dose of 3900 mg when they were challenged following 4–22 months on a maintenance daily dosing of 300 mg of peanut protein. In terms of adverse effects, 92% of patients experienced adverse symptoms during the initial-day escalation, 46% during the buildup period and 3.5% during home dosing. These allergic side effects were mostly mild and involved the skin and upper airways. Only two subjects received epinephrine after one home dose each. While peanut OIT was shown to be safe in this open-label cohort [64], it must be mentioned that four subjects withdrew from the study because of allergic reactions to OIT that persisted despite dose reduction. This reinforces the fact that peanut OIT may not be tolerated by all subjects. By 6 months, immunologic changes associated with this desensitization, such as decreased skin-prick tests and basophil hypersensitivity, were evident [65]. By 12–18 months, peanut-specific IgE levels decreased and peanut-specific IgG4 antibody levels increased significantly. The epitope-specific nature of the responses appeared to show a shift from IgE to IgG4, so that the IgG4 was directed at the same epitopes that were binding IgE prior to initiation of peanut OIT [60]. At 12 months of OIT, numbers of CD4+, CD25+, FoxP3+ Tregs were increased, but began to return to baseline by 18 months [66]. It is hypothesized that this transient increase in Tregs is what may drive the suppression of the Th2 response to peanut allergens, and indeed, Th2 cytokines were shown to be decreased after peanut OIT in this study [60].

Subsequent studies have also shown that desensitization can be accomplished by peanut OIT [65,66]. Blumen et al. reported results of an uncontrolled study of peanut OIT in 23 children, whose peanut allergy was confirmed by means of DBPCFC prior to initiating OIT with roasted peanut [66]. This study showed a highly significant increase in threshold of peanut challenge following OIT in 14 of 23 (60%) subjects who reached a maintenance dose of 500 mg of peanut. Immunologic parameters revealed a significant increase in peanut-specific serum IgG4 and a decrease in peanut-specific IL-5, IL-4 and IL-2 production by peripheral blood mononuclear cells in vitro after OIT [66].

Anagnostou et al. treated 22 peanut-allergic children whose peanut allergy was confirmed with an entry oral peanut challenge, with an open peanut OIT protocol [67]. In contrast to previous OIT studies, this protocol omitted the initial rush dose-escalation day and treatment began with gradual biweekly dose escalation until a targeted maintenance dose of 800 mg of peanut protein was reached. Nineteen subjects tolerated the maintenance dose and when challenged after approximately 30 weeks of maintenance therapy, the mean tolerated dose was increased by 1000-fold compared with baseline challenges. Sixty four percent (14 out of 22) subjects passed a 6600-mg peanut challenge with no symptoms, while four out of 22 subjects experienced mild or moderate symptoms. One patient dropped out during the dosing phase and two patients were unable to reach the 800-mg maintenance dose.

In 2011, Varshney et al. published the results of the first double-blind, placebo-controlled study of peanut OIT in which...
28 children were enrolled [68]. Sixteen of 19 subjects (84%) completed 12 months of peanut OIT treatment (maintenance dose: 4000 mg of peanut protein). This study showed that 100% of subjects reaching maintenance (16 out of 19) were able to successfully pass a 5000-mg peanut oral food challenge. Three out of 19 subjects (16%) were unable to complete the protocol (two out of 19 failed the initial dose-escalation day, and one out of 19 dropped out after the first gradual dose escalation). Overall in this study, peanut OIT was well tolerated by subjects, and no peanut OIT subjects required epinephrine treatment with dose-escalation visits or home OIT doses. Immunologic studies showed a decrease in skin prick testing, a transient increase then decrease in peanut-specific IgE and an increase in peanut-specific IgG4. In addition, peanut OIT was able to result in a decrease in Th2 cytokines (IL-5 and IL-13), with an increase in FoxP3hi:FoxP3intermediate CD4+ CD25+ T cells at the time of oral food challenge.

These studies suggest that peanut OIT is a safe and effective therapy that can induce desensitization with ongoing therapy. As outlined earlier, mechanistic data from various studies (Table 1) suggest a shift in allergen-specific cytokine production from a Th2 to a Th1 profile, also pointing towards concurrent immunomodulation. While these results with desensitization are encouraging, little is known about long-term safety, efficacy and most importantly development of clinical tolerance, which would be the ultimate goal of such therapy. It is also important to keep in mind that some subjects are unable to endure the allergic side effects associated with peanut OIT, indicating that this therapy may not be appropriate for all peanut-allergic individuals. The major side effects with OIT are related to reports of approximately 10–20% of subjects across different studies who have been unable to reach the maintenance phase of OIT because of gastrointestinal symptoms, which also highlights the concerns for eosinophilic esophagitis with OIT [69–71]. Based on these concerns, it must be emphasized that peanut OIT is not yet ready for practical everyday use in the clinic setting.

Peanut sublingual immunotherapy

Sublingual immunotherapy (SLIT) involves administration of small drops of allergen extract under the tongue, which are then swallowed (or in some studies spit out). SLIT has been used effectively in Europe for a number of years for the treatment of allergic rhinitis [72,73]. The typical dose of peanut protein used in studies of peanut SLIT is approximately 1000-times less compared with peanut OIT [74]. In 2011, Kim et al. published the results of the first double-blind study of peanut SLIT in which 18 peanut-allergic children were enrolled and underwent dose escalation to a maintenance dose of 2 mg of peanut protein [74]. After 12 months of treatment, subjects on active treatment (n = 11) consumed a median of 1710 mg peanut protein during oral food challenge (although the amount tolerated by those in the active treatment varied significantly), while placebo subjects (n = 7) ingested 85 mg before having an allergic reaction. There were no dropouts from adverse events related to peanut dosing during this study and side effects were mainly oropharyngeal symptoms, observed with 11.5% of active and 8.6% of placebo doses. As with OIT, peanut SLIT was associated with decreases in skin-prick tests and basophil activation assays [Table 1]. Immunologic studies revealed a transient increase in peanut-specific IgE levels over the first 4 months, which then steadily decreased, and a significant increase in peanut-specific IgG4. Th2 cytokines (IL-5 and IL-13) were decreased in those on active treatment with peanut SLIT, and this was not observed in placebo subjects.

Kulis et al. published a study exploring the mechanism of SLIT in which they showed that persistent mucosal exposure of peanut SLIT led to a rise in peanut-specific salivary IgA, further correlating this increase with results of oral food challenges in subjects (p = 0.0011) [75]. Peanut-specific salivary IgA has been thought to block antigen uptake and studies are ongoing to investigate this further.

In a recently published randomized, double-blind, placebo-controlled multicenter trial of peanut SLIT with a crossover design in which 40 subjects (age: 12–37 years) were enrolled, Fleischer et al. showed that after receiving 44 weeks of peanut SLIT, 14 out of 20 (70%) subjects were able to consume tenfold more peanut protein than baseline oral food challenge (median successfully consumed dose increased from 3.5 to 496 mg) [76], compared with three out of 20 (15%) subjects receiving placebo. After 68 weeks of SLIT, the median successfully consumed dose increased to 996 mg compared with 496 mg at the 44-week time point (p = 0.05). This study demonstrated that peanut SLIT was well tolerated, with mainly oropharyngeal symptoms as the notable adverse effects in this study. While encouraging, these results show only a modest level of desensitization with peanut SLIT, compared with results that have been demonstrated with peanut OIT.

While there is evidence that peanut SLIT is safe and has a beneficial treatment effect in peanut-allergic subjects, the level of desensitization achieved may not be as robust as seen with peanut OIT. However, it may serve as a viable option in subjects who cannot tolerate peanut OIT, given the low dose of peanut allergen required in treatment with peanut SLIT.

Peanut epicutaneous therapy

Epicutaneous therapy (EPIT) for peanut allergy consists of a small amount of peanut allergen delivered through a patch that is applied to the skin. EPIT has been shown to have some success in treatment of milk allergy based on results from a small pilot study [77], with common side effects mainly being pruritus and eczema at the site of application of the patch. This type of treatment for peanut allergy has been studied in murine models [78], and Phase II clinical trials of peanut EPIT are currently ongoing [101,102]. This therapy offers the advantage of an alternative route for delivery of peanut allergen; however, further studies are clearly needed to determine the efficacy and safety of this therapy.

Immunotherapy with modified recombinant food proteins

Immunotherapy with modified recombinant food proteins involves delivery of allergenic proteins that have undergone point mutations of key amino acid sequences, resulting in alteration of IgE-binding
allergic epitopes [59]. This technique has been found to decrease/inhibit IgE antibodies that bind with major peanut allergens [79].

Bacterial adjuvants have been used to increase the effects of modified recombinant protein immunotherapy and this has been the focus of several studies. Li et al. used subcutaneous heat-killed Listeria monocytogenes and the modified peanut proteins (mAra h 1, 2 and 3) in a peanut-sensitized mouse model and showed a marked decrease in incidence and severity of peanut-induced anaphylaxis compared with control mice [80]. This was thought to occur due to a shift from Th2 towards a Th1 profile based on decrease in IL-5 and IL-13 and increased levels of IFN-γ in the treated mice. Next, preliminary testing in mice was initiated to investigate if heat-killed Escherichia coli could serve as an effective adjuvant when combined with modified peanut proteins. Administration of heat-killed E. coli through the subcutaneous route led to skin inflammation [55]; hence, subsequent studies focused on investigating rectal administration of heat-killed E. coli-mAra h 1, 2 and 3 in peanut-sensitized mice [55,81]. Mice challenged with peanut had decreased severity of anaphylaxis, and splenocytes from these mice showed a trend towards deviation from a Th2 to a Th1 cytokine profile. Currently, a vaccine for humans, EMP-123, is in Phase I clinical trials [83]. While the prospect of development of a vaccine for peanut allergy is encouraging, additional studies are needed to investigate this further.

**Advances in treatment of peanut allergy: allergen-nonspecific approaches**

**Anti-IgE monoclonal antibodies**

The concept of nonspecific immunomodulation for peanut allergy has been studied with humanized monoclonal murine anti-IgE IgG1 antibodies that bind to IgE with high affinity, hence preventing IgE from binding to FcεRI receptors on mast cells and basophils. Anti-IgE therapy results in decrease in free IgE, which subsequently leads to downregulation of the FcεRI receptors on the surface of mast cells and basophils [82].

In 2003, Leung et al. reported the results of a randomized, double-blind, placebo-controlled study in which 84 challenge-confirmed peanut-allergic subjects were assigned to receive therapy with either placebo or 150, 300 or 450 mg of an experimental anti-IgE drug called TNX-901 (also known as Hu-901) subcutaneously, once a month for four doses [82]. Results showed that only the highest dose of 450 mg of this drug resulted in a statistically significant improvement, increasing the reaction threshold to peanut from 178 to 2805 mg. Approximately 25% of subjects treated with the highest dose of this drug showed no change in their threshold for peanut consumption, hence suggesting that this therapy would not be able to benefit all peanut-allergic subjects.

A separate randomized, double-blind, placebo-controlled Phase II trial of a different anti-IgE humanized IgG1 molecule omalizumab (Xolair®, Novartis, NJ, USA) in peanut-allergic subjects was prematurely terminated because of two serious allergic reactions that raised safety concerns during entry peanut challenge (prior to the administration of study drug) [83]. Sampson et al. recently published results from the 14 patients who completed 24 weeks of therapy followed by a second DBPCFC [83]. Preliminary data suggested that subjects receiving Xolair had a

**Table 1. Immunologic changes seen with peanut oral immunotherapy and peanut sublingual immunotherapy.**

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<th>Study (year)</th>
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<th>Immunologic changes</th>
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<td>Jones et al. (2009)</td>
<td>1–16</td>
<td>6 months: ↓ skin prick tests</td>
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<td>6–12 months: ↑ IL-5, IL-10, IFN-γ and TNF-α</td>
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<td>12–18 months: ↓ peanut-specific IgE, ↑ peanut-specific IgG4</td>
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<td></td>
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<td>12 months: ↑ numbers of CD4+, CD25+, FoxP3+ Tregs</td>
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<td>18 months: ↓ numbers of CD4+, CD25+, FoxP3+ Tregs and return to baseline</td>
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<td>T-cell microarrays showed downregulation in apoptosis-related gene expression</td>
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<td>Peanut SLIT</td>
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↑: Increase; ↓: Decrease; OIT: Oral immunotherapy; SLIT: Sublingual immunotherapy.

References:

[55], [63], [66], [68], [74], [83]
trend towards greater tolerated dose of peanut protein than in the placebo-treated group (p = 0.054). Given that the study was initially powered to enroll 150 subjects, it is not surprising that the results did not reach statistical significance.

Anti-IgE therapy for peanut allergy clearly remains a therapy that warrants further study. If used in combination with peanut OIT, particularly as supplemental therapy during the dose-escalation phase of immunotherapy, it could potentially have the advantage of decreasing allergic reactions during peanut dosing. Phase I/II studies of Xolair in combination with peanut OIT are currently ongoing [104].

**Chinese herbal medicine**

Herbs have been used for centuries in traditional Chinese medicine to treat a variety of ailments; however, they have not been used previously for treatment of food allergies. The Food Allergy Herbal Formula (FAHF)-1 was developed using the extracts of 11 herbs with anti-inflammatory properties, which have been used for hundreds of years by practitioners of traditional Chinese medicine to treat conditions such as asthma and gastroenteritis [84].

Li et al. showed that FAHF-1 blocks peanut-induced anaphylaxis in a murine model [85]. A simplified formula called FAHF-2 consisting of nine herbs was subsequently developed and results similar to the previous study were seen regarding reduction of anaphylaxis in peanut-sensitized mice [86]. In addition, mechanistic studies showed significantly decreased levels of plasma histamine, peanut-specific IgE and Th2 cytokines (IL-4, IL-5 and IL-13) in FAHF-2 treated mice, with significantly increased levels of IFN-γ, suggesting a shift from Th2 to Th1 cytokine profile.

A Phase I, randomized, double-blind, placebo-controlled, dose-escalation study in 19 human subjects with peanut and tree nut allergy demonstrated that FAHF-2 was safe and well tolerated during 7 days of therapy [87]. In terms of adverse effects, one subject in the FAHF-2 group and one subject in the placebo group reported only mild gastrointestinal symptoms. In an extended Phase I study, Patil et al. showed that daily dosing of FAHF-2 was safe and tolerated well by subjects [88]. Srivastava et al. showed that in mice, a butanol-extracted version of FAHF-2 reduced the volume of the dose by approximately fivefold but was able to maintain its efficacy [89]. This would be an important application for human subjects, given that the large tablet load of FAHF-2 (ten tablets three-times a day) is a barrier to compliance and serves as a potential limitation for this therapy. Srivastava et al. recently investigated the use of FAHF-2 in a murine model of multiple food allergies, showing that FAHF-2 was able to block anaphylaxis from three food allergens (peanut, codfish and egg) after sensitized mice were treated with FAHF-2 for 7 weeks [90]. A multicenter, double-blind, placebo-controlled Phase II trial of FAHF-2 is currently ongoing [105].

The concept of using Chinese herbal medicine and the development of FAHF-2 is one of the most exciting advances in the field of food allergy. It has been found to be safe and well tolerated in humans and offers the additional advantage of potentially treating multiple food allergies with one therapy.

**Expert commentary & five-year view**

The diagnosis and treatment of peanut allergy is an area that has eluded allergists for years. Millions of individuals suffer from peanut allergy, and while the prevalence of peanut allergy continues to increase, there is currently no approved treatment.

The accurate diagnosis of peanut allergy remains a critical first step in order to correctly identify subjects at risk for having an allergic reaction. However, none of the current diagnostic tools have been able to achieve sufficiently high predictive values to allow any one test to serve as an accurate diagnostic modality. While DBPCFC remains the gold standard for diagnosis, these remain difficult for clinicians to conduct routinely in the office setting. Recently, several studies have suggested that component-resolved diagnostics could improve the specificity of peanut allergy testing and have shown that compared with whole peanut-specific IgE levels currently used for in vitro testing, Ara h 2-specific IgE levels provide higher accuracy in diagnosing peanut allergy. While component-resolved diagnostics might be used as a supplement to existing diagnostic tests for peanut allergy, it does not appear to be ready to replace them at this time. The new molecular diagnostic techniques that are being studied are promising, but before they can be implemented in the clinical setting, these assays will need to be studied in larger clinical trials and validated against the current gold standard.

While not ready for prime time, combining component-resolved diagnostics, IgE epitope mapping and high-throughput microarray platforms may in the future allow for an assay that will result in better diagnostic capability and help identify patients at risk of persistent allergy.

There is a strong recognition of the unmet need to develop effective treatments for peanut allergy and much progress has been made in the development of novel therapies. Several studies have shown the safety and efficacy of peanut OIT and demonstrated its ability to induce desensitization with ongoing therapy, with immunologic changes during peanut OIT showing a shift in allergen-specific cytokine production away from a Th2 profile and also pointing towards concurrent immunomodulation. While desensitization would be able to provide much needed protection against accidental peanut ingestion, the ultimate goal of peanut OIT would be to help subjects achieve long-term clinical and long-lasting immunologic tolerance, which still needs to be investigated. There is evidence that peanut SLIT is safe, efficacious and well tolerated and may be a viable option in peanut-allergic subjects who cannot tolerate OIT, given the low dose of peanut allergen required in SLIT. However, the level of desensitization achieved may not be as robust as seen with peanut OIT. Anti-IgE therapy for peanut allergy clearly remains a therapy that warrants further study and might find a role as adjunct or supplemental therapy in combination with peanut OIT, and studies are ongoing to address this further. The application of Chinese herbal medicine and the development of FAHF-2 is perhaps one of the most exciting advances in the field. It has been found to be safe and well tolerated in humans and offers the additional advantage of potentially treating multiple food allergies with one therapy.
Recent advances in the diagnosis & therapy of peanut allergy

Review

It is important to note that many of the outlined studies for peanut allergy have limitations and this should be kept in mind when interpreting the literature. First, these studies exclude subjects with a history of previous anaphylactic reactions to peanut due to safety concerns, giving rise to the argument that individuals who possibly need these therapies the most are excluded from the outset. Including young children in whom remission of peanut allergy may occur during the study period may often confound studies. Given that many of the studies are pilot studies, the sample size is small and the lack of a placebo group makes it difficult to establish causality as a result of the therapy. While studies are currently ongoing, the development of prolonged true clinical tolerance to peanut as a result of any of these therapies has not yet been achieved; hence this remains a major clinical and research goal. This question would ideally be answered through conducting a prospective, randomized, double-blind, placebo-controlled trial that is powered to evaluate tolerance as the primary outcome.

Therefore, before any of these therapies can be implemented in clinical practice, many issues need to be addressed and, large, well designed, randomized, double-blind, placebo-controlled clinical trials are needed to determine risks that may be associated with ongoing therapy, optimal dosing regimens, efficacy and dosing for different age groups, ideal duration of therapy and appropriate patient selection for different therapies.

In conclusion, several treatment modalities for peanut allergy are showing promise, in the hands of experienced investigators for different therapies.

Key issues

- A double-blind placebo-controlled oral food challenge is the gold standard for diagnosis of peanut allergy.
- While not ready for prime time, combining component-resolved diagnostics, IgE epitope mapping and high-throughput microarray platforms may in the future allow for an assay that will result in better diagnostic capability and help identify patients at risk of persistent allergy.
- Peanut oral immunotherapy (OIT) has been shown to be relatively safe and efficacious and has demonstrated its ability to induce desensitization with ongoing therapy, with immunologic parameters showing a shift in allergen-specific cytokine production away from a Th2 profile.
- Peanut sublingual immunotherapy is safe and may be a viable option in peanut-allergic subjects who cannot tolerate OIT; however, the level of desensitization achieved may not be as robust as seen with peanut OIT.
- Anti-IgE therapy for peanut allergy remains a therapy that warrants further study and might find a role as adjunct or supplemental therapy in combination with peanut OIT.
- The application of Chinese herbal medicine and the development of Food Allergy Herbal Formula-2 is one of the most exciting advances in the field, offering the advantage of potentially treating multiple food allergies with one therapy.
- While not ready for prime time, combining component-resolved diagnostics, IgE epitope mapping and high-throughput microarray platforms may in the future allow for an assay that will result in better diagnostic capability and help identify patients at risk of persistent allergy.
- There is currently no approved treatment available for peanut allergy and none of the above experimental therapies are ready for everyday use in clinical practice. Data are lacking regarding long-term safety and efficacy.

References


Financial & competing interests disclosure

AW Burks is on the boards of the American Academy of Allergy, Asthma and Immunology and the Food Allergy & Anaphylaxis Network; is on the Medical Advisory Board for the Food Allergy Initiative; is a study section member for the NIH Hypersensitivity, Autoimmunity and Immune-Mediated section; and serves on Merck’s US Allergy Immunotherapy Allergist Advisory Board. He also serves as a consultant for Dow AgroSciences, Dynavax Technologies Corp, ExploraMed Development, LLC, Genalyte, Hycor Biomedical, Merck, Nordic Biotech Advisors ApS and PBN Nutritional. He is a minority stockholder of Allertein, a speaker for Mylan Specialty and has received royalties from UpToDate. AW Burks holds grants from the NIH and Wallace Research Foundation. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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