

## State of the art on food allergen immunotherapy: Oral, sublingual, and epicutaneous

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**IgE-mediated food allergy is a global health problem that affects millions of persons and affects every aspect of life for the patient. Developing effective treatment strategies to augment current practice standards of strict dietary avoidance of antigens and availability of self-injectable epinephrine has been a major focus of research teams, advocacy groups, funding agencies, and patients and their families. Significant progress has been made through the development of allergen-specific immunotherapy encompassing 3 major forms of treatment: oral, sublingual, and epicutaneous immunotherapy. These**

**therapies are in various stages of clinical investigation, with some successes noted in clinical outcomes and modulation of immune mechanisms toward effective therapy. Here we review recent progress and areas of concern for the role of these forms of immunotherapy as an emerging treatment for food allergy. (J Allergy Clin Immunol 2014;133:318-23.)**

**Key words:** Food allergy, immunotherapy, treatment, investigational

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Food allergy affects 15 million Americans and numerous children and adults throughout the world, with more than 170 foods reported to cause food-induced allergic reactions.<sup>1</sup> The health and economic effect of food allergy is vast and growing not only because of the cost of health care expenditures but also the effect on the workplace, food industry, food regulatory agencies, and, importantly, patients and their families, whose lives are affected daily. Developing effective treatment strategies outside of dietary avoidance of antigens and availability of self-injectable epinephrine<sup>1</sup> has been a high priority for families, advocacy groups, funding agencies, and research teams. Significant progress has been accomplished over the past 5 years, with the primary focus on allergen-specific immunotherapy encompassing 3 major forms of treatment: oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT). Each of these forms of immunotherapy is in different stages of investigation with similar immunologic targets (Fig 1). These therapies differ in route of administration, dose of antigen, and clinical research outcomes (Table I). This review will highlight the accomplishments and challenges of these investigational approaches.

### OIT

OIT has been studied for more than a decade in clinical trials and has the largest body of evidence among emerging therapies for food allergy. OIT is associated with both short-term and longer-term responses to therapy, but OIT also has limitations caused by safety issues. The presumed mechanism of action for OIT is activation of gut mucosal dendritic cells, which affect the allergic response through immunomodulation of tissue and circulating effector cells.<sup>2</sup> Other mechanisms have been shown to be important, including modulation of IgE responses, such as reductions in the amount of specific IgE and changes in repertoire diversity and associated polyclonal increases in specific IgG<sub>4</sub> levels,<sup>3</sup> as well as IgE receptor pathway suppression of basophils.<sup>4</sup> Current OIT protocols typically include 3 phases requiring ingestion of allergen-specific flour in a food vehicle: (1) modified rush desensitization (initial escalation) with 6 to 8 doses of

# Abbreviations used

|        |                                     |
|--------|-------------------------------------|
| AE:    | Adverse event                       |
| CoFAR: | Consortium of Food Allergy Research |
| DBPC:  | Double-blind, placebo-controlled    |
| EPIT:  | Epicutaneous immunotherapy          |
| OFC:   | Oral food challenge                 |
| OIT:   | Oral immunotherapy                  |
| SLIT:  | Sublingual immunotherapy            |
| SPT:   | Skin prick test                     |
| Treg:  | Regulatory T                        |

allergen given rapidly during day 1; (2) build-up dosing under observation every 1 to 2 weeks until a target dose is reached (over 6-12 months); and (3) daily home maintenance dosing (typically years). Oral food challenge (OFC) is used to assess the allergen reactivity threshold during evaluation of clinical desensitization (during therapy) and functional tolerance (while off therapy on diet restriction).

Recent randomized, controlled, multicenter clinical trials have provided valuable efficacy and safety data for evaluation of OIT as an active treatment.<sup>5-11</sup> In a trial of peanut OIT, 28 children (age, 1-16 years) were randomized to receive peanut OIT (4000 mg) versus placebo OIT.<sup>7</sup> Peanut OIT was associated with increased peanut consumption compared with placebo after 12 months (5000 vs 280 mg,  $P < .001$ ), and findings of decreased skin prick test (SPT) size and  $T_H2$  cytokine levels and increased peanut-specific IgG<sub>4</sub> levels and regulatory T (Treg) cell numbers. Similar findings were noted during a milk OIT trial in 20 children with milk allergy (age, 6-21 years) randomized to milk OIT (500 mg) versus placebo OIT.<sup>6</sup> After 6 months, the change in reaction threshold was 5100 versus 0 mg in the OIT ( $P = .002$ ) and placebo ( $P = .16$ ) groups, respectively. Other randomized controlled trials for milk OIT in children have shown similar clinical findings.<sup>8-11</sup> In a study from the Consortium of Food Allergy Research (CoFAR), 55 children with egg allergy (age, 5-18 years) were randomized to egg versus placebo OIT.<sup>5</sup> In 40 subjects receiving egg OIT, 55% passed a 5-g OFC at 10 months versus 0% of placebo-treated subjects (dose consumed, 5000 vs 50 mg;  $P < .001$ ); 75% of subjects receiving egg OIT passed a 10-g OFC at 22 months. Desensitization was associated with reduced egg-specific IgE and increased IgG<sub>4</sub> levels at 10 months and reduced basophil activation and SPT sizes at 22 months. These studies highlight the efficacy of allergen-specific OIT in the induction of clinical desensitization and treatment-specific immunomodulation. The role of multiallergen OIT with different foods given at the same time and the utility of OIT for other food allergens, such as tree nuts and seeds, are also under investigation.

Several studies have evaluated short-term tolerance or sustained unresponsiveness after years of therapy, as defined by discontinuation of OIT for 1 to 6 weeks before an OFC.<sup>5,12-14</sup> In an open-label study of 6 children with egg allergy (age, 3-13 years), all 6 passed the OFC and introduced egg into their diet after 33 months of OIT (median dose, 2400 mg).<sup>13</sup> Similarly, after 5 years receiving 4000 mg of peanut OIT, 50% of subjects passed a tolerance OFC and incorporated peanut *ad libitum* into their diets.<sup>14</sup> Treatment successes were associated with reduced peanut-specific IgE and Ara h 1 and Ara h 2 levels and SPT responses when compared with treatment failures, parameters that were predictive of outcomes. In a trial comparing milk OIT and

SLIT over 60 weeks, tolerance OFCs were performed after 1 and 6 weeks off therapy in subjects demonstrating desensitization at week 60.<sup>12</sup> Among OIT-treated subjects, 10% failed at week 1, and 20% failed at week 6. In the CoFAR egg OIT trial, 27.5% passed an OFC assessing "sustained unresponsiveness" at 24 months<sup>5</sup> and continued egg *ad libitum* through 30 to 36 months. In a follow-up survey conducted 3 to 4 years after dose escalation in subjects successfully treated with milk OIT, 22% reported limiting milk consumption because of symptoms.<sup>15</sup> Among subjects receiving peanut OIT with evidence of sustained unresponsiveness, survey findings after 3 to 4 years revealed that none of those subjects reported symptoms with *ad libitum* peanut consumption.<sup>14</sup> Overall, short-term tolerance or sustained unresponsiveness is possible in a subset of subjects, but further investigation is needed to better understand the long-term effect of treatment. The Immune Tolerance Network IMPACT trial is evaluating long-term tolerance among children with peanut allergy (age, 1-4 years) in a randomized 3-year peanut OIT trial to further address this issue.

Although OIT has demonstrated clinical efficacy for desensitization, meta-analyses highlight the fact that insufficient data exist for full efficacy assessments and that safety concerns persist and require further evaluation.<sup>16-20</sup> Generally, side effects associated with OIT treatment trials are mild to moderate, predominantly oropharyngeal, and easily treated<sup>5-7,21,22</sup>; however, more severe reactions, such as generalized urticaria/angioedema, wheezing/respiratory distress, laryngeal edema, and repetitive emesis, have been reported. Currently, the most limiting allergic side effect is that approximately 10% to 15% of subjects treated with OIT experience gastrointestinal symptoms preventing continuation of therapy.<sup>23</sup> Induction of eosinophilic esophagitis has been reported.<sup>24</sup> During peanut OIT,<sup>7</sup> symptoms of some degree were noted in the many subjects undergoing active treatment. During initial-day escalation, 2 subjects withdrew and 47% experienced side effects requiring antihistamines, with 2 also requiring epinephrine. Symptoms were noted after 1.2% of 407 build-up doses; however, 16 of 19 subjects receiving active OIT reached a daily 4000-mg maintenance dose with minimal side effects. Similarly, with milk OIT, 45.4% of OIT doses were associated with symptoms compared with 11.2% of placebo doses, most of which were mild and oropharyngeal.<sup>6</sup> Epinephrine administration was required after 4 OIT doses. During year 1 of egg OIT, 75% of 11,860 OIT doses were symptom free versus 96% of 4018 placebo doses.<sup>5</sup>

Viral infections, menses, and exercise have also been associated with decreasing the reaction threshold for subjects receiving stable OIT dosing,<sup>25</sup> further complicating current dosing regimens and often requiring dose adjustments in the face of acute illness.<sup>21</sup> In a long-term follow-up study of milk OIT, 22% of subjects who had previously completed OIT and passed a tolerance OFC reported limitation of milk consumption because of symptoms often related to exercise (25%) and illness (6%).<sup>15</sup> The implementation of rush OIT protocols designed to shorten the interval to maintenance therapy has been associated with increased adverse symptoms and epinephrine use.<sup>8,21,26,27</sup> Omalizumab treatment before and during OIT was associated with some reduction in side effects and reduced time to target dose in a pilot study of 11 subjects with milk allergy.<sup>28</sup> Similar findings were noted in a recent pilot study of omalizumab paired with OIT in 13 children with peanut allergy, with evidence of higher dosing acquired during rush desensitization and reduced

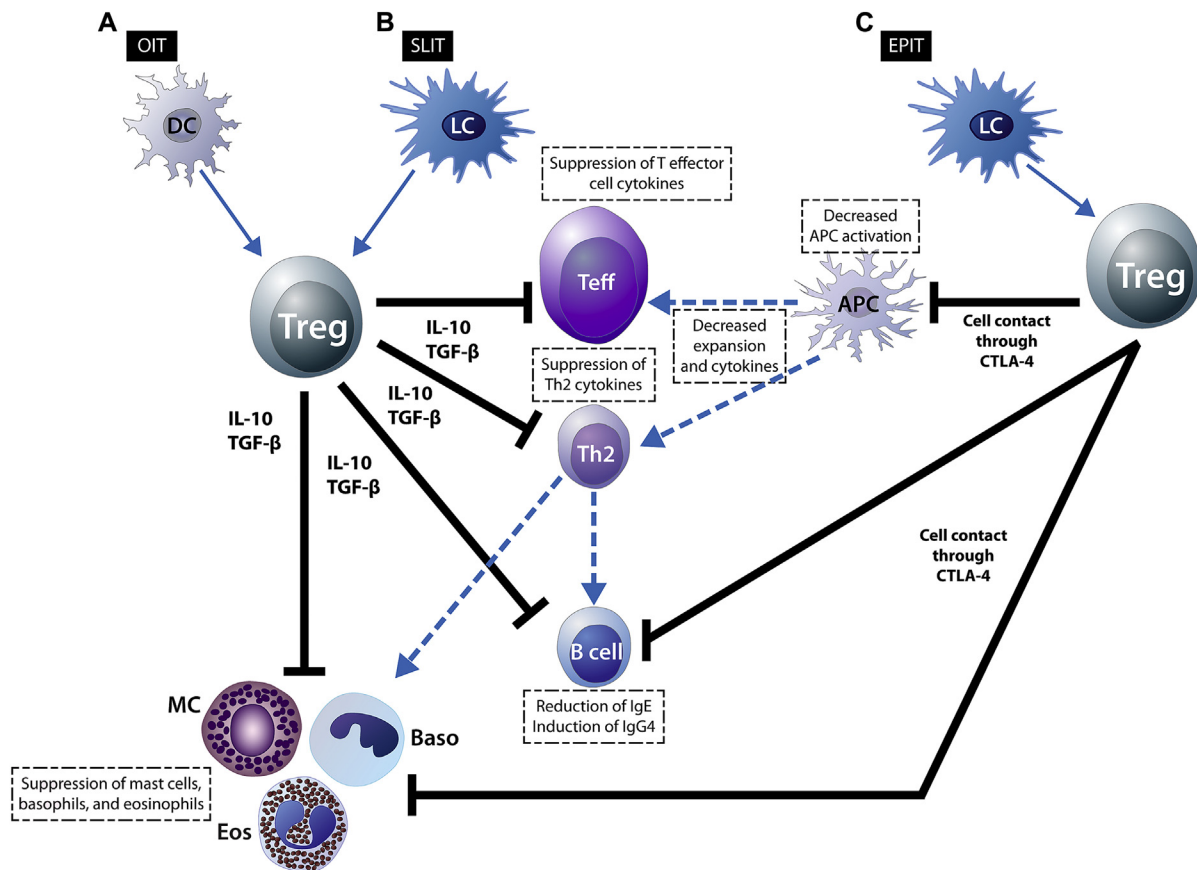


**FIG 1.** Possible mechanisms for different forms of food allergen immunotherapy. Food allergen immunotherapy affects the food-induced allergic response through interaction of tissue-specific innate immune cells and modulation of adaptive immune pathways, leading to suppression of a variety of effector cell functions. **A**, OIT works primarily through allergen activation of dendritic cells in the gut mucosa, resulting in effector cell modulation. **B**, SLIT works through allergen interaction with protolerogenic Langerhans cells in the oral mucosa, leading to downregulation of the allergic response. **C**, EPIT works through allergen capture by Langerhans cells in the epidermis and a subpopulation of dendritic cells expressing the langerin-specific surface marker cytotoxic T lymphocyte-associated antigen 4 (*CTLA-4*), which migrate to regional lymph nodes to affect immune activation. *APC*, Antigen-presenting cell; *Baso*, basophil; *DC*, dendritic cell; *Eos*, eosinophil; *LC*, Langerhans cell; *MC*, mast cell; *Teff*, effector T.

time to target dosing. Adverse reactions were still noted in both pilot studies, some requiring epinephrine administration.<sup>29</sup> Additional studies are needed to improve the safety profile before OIT can be sanctioned and encouraged for widespread use.<sup>16-20</sup>

A possible alternative to OIT is the use of heated allergen for the treatment of milk allergy, egg allergy, or both because of temperature-associated changes in protein conformation and reduced IgE binding of heated allergen. Clinical trials performed in children with milk<sup>30</sup> and egg<sup>31</sup> allergy have demonstrated that approximately 70% to 80% of children with milk or egg allergy safely ingest baked milk or egg products.<sup>30,31</sup> The consumption of 1 to 3 servings of baked allergen products daily was associated with accelerated tolerance development when compared with age-matched control subjects.<sup>32</sup> Reduced specific IgE levels and SPT responses and increased IgG<sub>4</sub> levels and activated Treg cell numbers are noted with favorable clinical responses.<sup>31-33</sup> An ongoing CoFAR-sponsored study comparing OIT and baked egg treatment for patients with egg allergy will provide important information about the treatment effects of these therapies. Current data suggest that ingestion of baked milk and egg is safe in a large

proportion of patients and might provide a therapeutic advantage toward tolerance development.

## SLIT

With SLIT, patients take gradually increased doses of allergen extract that are placed under the tongue and then spit or swallowed. It is thought that SLIT works through allergen interaction with protolerogenic Langerhans cells in the oral mucosa, which leads to downregulation of the allergic response.<sup>34,35</sup> For the treatment of asthma and allergic rhinitis, SLIT can improve clinical symptoms and has a favorable safety profile.<sup>36-38</sup>

SLIT is not currently recommended for treatment of food allergy, but it has been successful in causing desensitization to food allergens in clinical trials. As with OIT, SLIT protocols include escalation and maintenance dosing, although in SLIT the doses of allergen administered are smaller, generally less than 10 mg/d. The first published reports of SLIT for food allergy appeared more than a decade ago, when SLIT for kiwi allergy was described in a case report in which a patient with a history of multiple anaphylactic reactions to the fruit was desensitized.<sup>39</sup>

**TABLE I.** Comparison of food allergen immunotherapy currently in clinical trials

|                      | OIT                                                                         | SLIT                    | EPIT                                                     |
|----------------------|-----------------------------------------------------------------------------|-------------------------|----------------------------------------------------------|
| Daily dose (protein) | 300-4000 mg                                                                 | 2-7 mg                  | 50-500 µg                                                |
| Side effects         | Gastrointestinal, oral (systemic when associated with fever, URI, exercise) | Oral-pharyngeal (local) | Skin (local)                                             |
| Desensitization      | Large effect                                                                | Moderate effect         | Ongoing investigation                                    |
| Long-term tolerance  | Variable response                                                           | Ongoing investigation   | Unknown                                                  |
| Immune modulation    | Significant                                                                 | Present                 | Present in mice; ongoing investigation in human subjects |

URI, Upper respiratory tract infection.

That patient subsequently underwent approximately 5 years of maintenance therapy and then ceased kiwi intake for 4 months but remained tolerant of the fruit.<sup>40</sup>

The case report of kiwi SLIT was followed by randomized, placebo-controlled studies of SLIT with hazelnut<sup>41</sup> and peach.<sup>42</sup> In the analysis of hazelnut SLIT, 22 adult patients received 8 to 12 weeks of SLIT with hazelnut or placebo.<sup>41</sup> In the subsequent food challenge almost half of the patients in the active treatment group consumed 20 g of hazelnut, whereas only 9% in the placebo group consumed 20 g of hazelnut. For peach SLIT, 49 adults patients underwent 6 months of therapy with peach (n = 33) or placebo (n = 16) extract.<sup>42</sup> During the posttherapy food challenge, the active treatment group tolerated 3-fold amounts of peach before undergoing nonlocal reactions than seen in the placebo group. In a non-placebo-controlled study of 8 children with cow's milk allergy, 6 months of milk SLIT led to an increase in the mean volume of milk that elicited allergy symptoms from 39 to 143 mL.<sup>43</sup> The change was unlikely to have been caused by the children outgrowing their milk allergy because they were all older than 6 years at the start of the study.

SLIT for cow's milk allergy has been compared with OIT in a group of 30 children (age, 6-17 years).<sup>12</sup> The children were randomly assigned to receive either SLIT only or SLIT followed by OIT at 2 different doses. After 60 weeks of maintenance therapy, 1 of 10 SLIT-only participants achieved desensitization to 8 g of milk protein, whereas 6 of 10 patients in the lower-dose SLIT/OIT group and 8 of 10 patients in the higher-dose SLIT/OIT group achieved desensitization. The SLIT-only group consumed more milk at the time of the OFC than at the beginning of the study, but overall, OIT led to more occurrences of systemic reactions than SLIT.

In the first study of SLIT for peanut allergy,<sup>44</sup> 18 children age 1 to 11 years received 12 months of SLIT with peanut or placebo. During dosing, side effects were minimal and primarily oropharyngeal, and treatment was not commonly required. In the subsequent food challenge, although the responses showed some individual variability, the treatment group safely ingested 20 times more peanut than the placebo group and had immunologic changes suggesting modification of the allergic response. A subsequent multicenter study of 40 patients with peanut allergy (age, 12-37 years) evaluated the efficacy of SLIT with peanut or placebo.<sup>45</sup> After 44 weeks of therapy, 14 (70%) of 20 patients who received active therapy were able to consume 5 g of peanut powder or at least 10-fold more peanut powder than at baseline, but only 3 (15%) of 20 patients receiving placebo showed a similar response.

A retrospective comparison study of patients with peanut allergy treated with either peanut OIT or SLIT indicated that after 12 months of therapy, patients who received SLIT reacted at lower

eliciting dose thresholds and were less likely to pass food challenges evaluating desensitization.<sup>46</sup> Thus available evidence for milk and peanut allergy suggest SLIT therapy is less effective than OIT for desensitization but has a better safety profile.<sup>12,46</sup>

As with studies of OIT, studies of SLIT have largely excluded patients with a history of severe reactions, such as anaphylaxis. Among patients who have undergone treatment, response has been variable, and currently, there are no validated methods of predicting response. Therefore the applicability of SLIT in the general population of patients with food allergy remains unclear. There are ongoing SLIT studies that should help us better understand the possible role of this type on therapy for food allergy.

## EPIT

EPIT uses a novel delivery of allergen to the skin surface through application of an allergen-containing patch to activate skin Langerhans cells, with subsequent migration to lymph nodes and downregulation of effector cell responses.<sup>35,47,48</sup> Preclinical studies in animals indicate a potential application in therapeutics. Although limited studies are currently published, peanut EPIT is currently under active clinical development in Europe and North America, with the goal of being available in clinical practice in the coming years.

A proof-of-principle study for use of EPIT in patients with food allergy was conducted in a 3-month pilot, double-blind, placebo-controlled (DBPC) trial in 18 children with milk allergy (age, 0.8-7.7 years).<sup>49</sup> Treatment consisted of three 48-hour patch applications on the back (skimmed milk powder as active substance) per week for 3 months. Adverse events (AEs) were mostly local erythema/eczema occurring at application sites and remaining visible for several days. The estimated risk of local eczema was higher in the active group than in the placebo group (odds ratio, 8.20; 95% CI, 2.72-24.5;  $P < .001$ ). The cumulative reactive dose of milk (baseline vs 3 months) was  $1.77 \pm 2.98$  versus  $23.61 \pm 28.61$  mL and  $4.36 \pm 5.87$  vs  $5.44 \pm 5.88$  mL ( $P = .13$ ) in the active and placebo groups, respectively. Overall, this first EPIT study in food allergy suggested an acceptable safety profile, and the clinical findings were considered encouraging.

A comprehensive clinical plan to develop EPIT for use in patients with peanut allergy was initiated. A randomized, DBPC, phase I safety trial in the United States included 80 peanut-treated subjects and 20 placebo-treated subjects. The peanut patch (DBV Technologies, Paris, France) proved safe and convenient for patients with nonsevere or severe peanut allergy up to the doses of 250 µg of peanut protein per patch in children and 500 µg of peanut protein in adolescents and adults during the 2 study weeks.<sup>50</sup> Overall, 2 of 80 subjects receiving active EPIT and 1 of 20 subjects receiving placebo EPIT dropped out prematurely for

AEs; 90% experienced mild or moderate local AEs, and systemic AEs were mostly mild and transient, with no severe AEs and no epinephrine use.

The first peanut efficacy trial (ARACHILD), a DBPC phase IIa study including 54 children with severe peanut allergy (age, 5-17 years) all treated with the peanut patch (100 µg of peanut protein) after 6 months of blinded therapy, is currently in progress in France. OFCs were conducted at 6-month intervals over an 18-month period to assess the reaction threshold. Safety data after 12 to 18 months were satisfactory and consistent with phase I results. Children showed consistent and sustained desensitization, with up to 67% responders (defined as  $\geq 10$ -fold increase in cumulative reactive dose from baseline) at 18 months and 4 subjects reaching 1.1 to 2.5 g of peanut protein (approximately 3.3-8 peanuts).<sup>51</sup> This study is ongoing and has been extended to 36 months of EPIT.

A large DBPC phase IIb dose-finding trial (VIPES) currently running in 22 centers in the United States and Europe has already enrolled 221 pediatric and adult subjects with a high level of peanut allergy for a 1-year treatment with peanut EPIT versus placebo EPIT. No safety concerns have been noted after up to 11 months of EPIT for the first enrolled subjects. Results are expected for late 2014, with a planned extension phase up to 36 months. Additionally, the CoFAR study group has initiated a randomized controlled study of peanut EPIT planned for 30 months of treatment with enrollment of 75 pediatric subjects.

Many preclinical studies suggest an original mechanism for EPIT. Mice sensitized to ovalbumin, peanut, or aeroallergens<sup>52</sup> were allocated to EPIT, SCIT, untreated, and negative control groups. After 8 weeks of weekly treatment, plethysmography after allergen aerosols showed decreased airway hyperreactivity with EPIT ( $P < .05$  vs the untreated groups) at similar levels as seen in the SCIT and negative control groups. Levels of specific sIgG<sub>2a</sub> for all allergens increased with EPIT, similarly to SCIT, whereas the IgE/IgG<sub>2a</sub> ratio decreased. EPIT also reversed airway hyperreactivity measured by resistance compliance, also similarly to SCIT.<sup>53</sup> In bronchoalveolar lavage fluid cytokine, eotaxin, and eosinophil values decreased with EPIT and SCIT ( $P < .001$  vs sham treatment).

An ovalbumin patch was applied on the intact skin of mice to study allergen migration with EPIT<sup>54</sup>; ovalbumin neither crossed passively through the skin nor was systemically delivered. Ovalbumin was taken up and internalized by dendritic cells in the superficial layers of the stratum corneum and transported to the draining lymph nodes more rapidly in sensitized than in naive mice. Repeated application downmodulated the immune responses and generated clearly tolerogenic Treg cells. Interestingly, this tolerogenic effect disappeared when EPIT was carried out on stripped skin.<sup>55</sup>

EPIT induces a specific and probably long-lasting population of Treg cells.<sup>56,57</sup> In murine peanut-induced eosinophilic disorders, depleting Treg cells with anti-CD25 antibody erased the effect of EPIT. Moreover, the protection offered by EPIT-induced Treg cells against peanut oral exposure could be adoptively transferred to sensitized but untreated animals.<sup>56</sup> This Treg cell population seems long-lasting.<sup>57</sup>

## CONCLUSIONS

New immunotherapeutic approaches to treating food allergy are being tested in clinical trials, with the majority focused on

IgE-mediated disease and prevention of anaphylaxis. Although these therapies have been met with some success defined by using a variety of parameters (eg, induction of desensitization and/or tolerance and/or immunomodulation), none are ready for widespread clinical use because of the uncontrolled nature of most of the trials, the small number of subjects studied in aggregate, selection biases within the studies, and uncertain safety profiles.<sup>16-20</sup>

The current modalities of investigation vary among treatment modalities. Currently, OIT and SLIT are being evaluated and advanced in clinical trials in academic centers, and global drug product development is being conducted for EPIT. More work is needed to ensure the balance of efficacy outcomes with long-term safety to shift the current state of clinical equipoise associated with food allergen immunotherapy.<sup>58</sup> Importantly, work is in progress toward improving our understanding of immune mechanisms important in food allergy and oral tolerance induction. An interesting paradox in performing and evaluating these studies is the balance of what parents most often want from treatment of a child with food allergy, which is clinical desensitization, and what investigators want, which is long-term and sustained tolerance. Most exciting is the fact that research is progressing to larger-scale trials that are required to determine the best therapy and most appropriate labeling for clinical use; these are projected to be several years from full realization. Future studies with these promising approaches to treatment, as well as other emerging immunomodulator therapies, are needed to provide effective, safe, and sustainable treatment options for children and adults with food allergy.

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