



Immunotherapy for food allergy

William R. Reisacher^{a,b} and Wesley Davison^{a,b}

Purpose of review

The current review discusses strategies for administering specific immunotherapy (SIT) for the treatment of food allergy. It focuses on three delivery routes for food allergens, immunomodulatory adjuvants and allergen modifications.

Recent findings

Interest in SIT for food allergy has been increasing significantly. Sublingual immunotherapy is effective for desensitization with a very favorable adverse event profile. Epicutaneous immunotherapy is also effective, most notably in younger children, with a high rate of local reactions. Oral immunotherapy demonstrates high efficacy, but with a higher risk of gastrointestinal and systemic adverse events. The need for long-term application to sustain desensitization is currently unclear. Immunomodulatory adjuvants may be added to enhance or diminish the immunogenicity of proteins, whereas genetic modifications of food allergens are designed to limit the risk of adverse reactions and address the issues of standardization and supply.

Summary

SIT for food allergy is reaching the point where it may soon be used routinely in clinical practice. Current research focuses on new delivery routes and methods to enhance the effectiveness of the therapy while minimizing the risk of adverse reactions. Future efforts are underway to determine the optimal dose for each delivery method and the length of maintenance dosing required to retain the protective effect.

Keywords

allergen, allergy, desensitization, food, immunotherapy

INTRODUCTION

Food allergy continues to be a growing concern in our society. The incidence is estimated to be as high as 8% in children and 5% in adults [1]. For reasons that are still unclear, the prevalence of food allergy in school-aged children rose 18% from 1997 to 2007 [2]. Reactions to food ingestion in a sensitized individual can range from oral itching or a mild skin rash to severe gastrointestinal reactions and life-threatening anaphylaxis [3]. This daily struggle can have a significant impact on the quality of life for those with food allergy and their families. Allergic children tend to have higher levels of anxiety and feelings of social isolation, which is only exacerbated by the physical isolation that is often implemented in the lunch-room setting [4]. Although some food allergies, such as those from cow's milk or egg, typically decrease throughout childhood, allergies to peanut have only a 20% chance of being outgrown [5,6].

The primary treatment for food allergy is limiting or modifying those foods that trigger mild, localized symptoms and strict elimination of foods that produce moderate-to-severe, immediate symptoms or systemic reactions. However, these dietary restrictions are often difficult for people to adhere

to, leading to accidental ingestion, which can be potentially life-threatening [7]. Young children may also be at risk for nutritional deficiencies if the diet is not closely monitored [8]. Oral antihistamines and auto-injectable epinephrine are used to delay the progression of symptoms until emergency care is reached, but cost and convenience are barriers to these options as well. It is estimated that every 6 min, someone visits an emergency department in the United States with anaphylaxis related to food allergy, and this highlights the need for better preventive strategies [9].

Although specific allergy immunotherapy (SIT) has been used for the long-term management of

^aDepartment of Otolaryngology, Head & Neck Surgery, Weill Cornell Medical College and ^bNewYork-Presbyterian Hospital, New York, New York, USA

Correspondence to William R. Reisacher, MD, FACS, FAAOA, Associate Professor, Department of Otolaryngology, Head & Neck Surgery, Weill Cornell Medical College, 1305 York Avenue, 5th Floor, New York, NY 10021, USA. Tel: +1 646 962 2093; fax: +1 646 962 0100; e-mail: wir2011@med.cornell.edu

Curr Opin Otolaryngol Head Neck Surg 2017, 25:000–000

DOI:10.1097/MOO.0000000000000353

KEY POINTS

- Oral immunotherapy is effective and improves quality of life, but due to safety concerns, therapies are being developed that reduce IgE antigenicity while maintaining T-cell epitopes.
- Sublingual immunotherapy is safer and more convenient than oral immunotherapy, but less effective.
- Viaskin is well tolerated and tolerable, but has a high rate of local skin reactions. Efficacy is best when used for 2 years in those less than 11 years of age.
- Adjuvants may be used to either enhance or diminish the immunogenicity of allergens.
- Peptide immunotherapy represents a potential future modality for desensitization to food allergens, even through the subcutaneous injection route.
- Recombinant food allergens are being investigated for both diagnostic and therapeutic purposes.

moderate-to-severe allergic rhinitis and allergic rhinoconjunctivitis caused by airborne allergens, it has not been routinely used for the treatment of food allergies [10,11]. Early experiments in the 1990s, using subcutaneous injections of aqueous peanut extract, demonstrated successful desensitization, but with an unacceptable level of severe, systemic reactions. The concept of SIT for foods was abandoned for the next decade until Mempel *et al.* [12] reported successful desensitization to kiwi in a 29-year-old woman using sublingual immunotherapy (SLIT) with liquid extract. Since then, desensitization to other allergens, including hazelnut, milk, peach and peanut, has been achieved using SLIT [13–17]. The goals of immunotherapy for food proteins are to provide a level of protection against accidental ingestion, not to facilitate regular usage equal to an individual who is not sensitized.

The use of SLIT for food allergies is attractive because of its enhanced safety profile, but efficacy is limited due to the amount of protein that can be delivered to the sublingual space with a dissolvable tablet or a small volume of liquid extract [18]. Achieving the desired daily dose might require multiple daily applications of a treatment, and liquid SLIT has already demonstrated a greater than 50% dropout rate during the 3-year maintenance phase when being used for peanut allergy [19]. This is particularly concerning because the necessary length of the maintenance phase, including the possibility of lifelong therapy, is currently unknown. This article focuses on the newer methods of delivering SIT for food allergy, along with the adjuvants and genetic modifications that

can render the treatment more effective and safer for extended use.

DELIVERY ROUTES FOR FOOD IMMUNOTHERAPY

Oral immunotherapy

Oral immunotherapy (OIT) uses ingestion of food protein, often using a rapid escalation phase, followed by daily maintenance as a disease-modifying treatment for food allergy [20].

An egg-containing biscuit for egg OIT demonstrated moderate efficacy, with 8/15 individuals tolerating an open boiled egg food challenge less than 1 year after induction [21]. In a randomized, double-blind, placebo controlled trial (RDBPCT) of 29 children, aged 1–5.5 years, given hydrolyzed egg, specific IgG₄ levels increased, whereas CD203c+/CD63+ basophils decreased significantly, compared with placebo [22]. A raw egg OIT study found that 27/28 individuals ate one whole egg at completion, with anaphylaxis in five during therapy. Pretherapy and posttherapy antigen-specific basophil activation with egg white, ovalbumin (OVA) and ovomucoid was significantly higher in children with both egg and other food allergies, compared with those with egg allergy alone. Specific IgE and spontaneous basophil activation both decreased after completing OIT, suggesting that basophil activation could be used to monitor the body's response to receiving OIT [23].

Serum immunoglobulins have shown promise in predicting sustained unresponsiveness following OIT. A randomized placebo-controlled trial of egg OIT found sustained unresponsiveness in 27.5% of individuals at 2 years and 50% sustained unresponsiveness by 4 years while receiving maintenance OIT. Sustained unresponsiveness achievers had significantly increased IgG₄ levels, compared with nonsustained unresponsiveness achievers, as well as a lower baseline ratio of specific IgE to total IgE (1.1 vs. 2.4%) [24]. A recent CoFAR trial found that pretreatment-specific IgE levels for egg white and ovomucoid were significantly lower in individuals who achieved sustained unresponsiveness at 4 years, thus representing potentially useful biomarkers [25]. In another study, 21/26 individuals were able to eat one hard-boiled egg after a 1-year maintenance phase. Predictors of sustained unresponsiveness included higher baseline ovomucoid, egg white and OVA-specific IgA and higher IgG₁ levels after the 1-day rush phase [26]. In a recent randomized double-blinded study of 9–36-month-old children given peanut OIT, sustained unresponsiveness was 78% overall at 4 weeks after stopping therapy, with

no significant difference between 300 and 3000 mg peanut OIT dosing. Children in the treatment group were 19 times more likely to pass an oral food challenge than controls [27[■]].

OIT safety remains a concern, and eosinophilic gastrointestinal disorders requiring food avoidance occur in 6.25% of OIT patients [28]. A study using dehydrated egg white for OIT in 28 individuals reported an adverse event rate of 21%, including one case of anaphylaxis [29]. Another recent study found that 4/68 children given cow's milk OIT developed anaphylaxis with just 2–4 ml of milk. Mild-to-moderate reactions were common but did not prevent completion of OIT [22]. One method to improve safety is by using omalizumab, an mAb that binds to IgE and blocks mast cell activation. A RDBPCT compared omalizumab with placebo in 7–32-year-olds who initiated milk OIT after 4 months of medication. Percentage of doses that caused adverse events and the number of adverse events requiring treatment occurred significantly less in the treatment arm (2.1 vs. 16.1% and 0.0 vs. 3.8%, respectively). Desensitization and sustained unresponsiveness were not significantly different [30[■]]. Similarly, 37 individuals, aged 7–25 years, were randomized to omalizumab or placebo for 12 weeks, then underwent weekly OIT until they achieved desensitization to 2 g peanut protein. Significantly, 6 weeks after stopping omalizumab, 79% of those individuals tolerated 2 g peanut protein, vs. 12% of the placebo group. There was trend toward lower adverse events in the treatment arm compared with placebo that did not reach significance ($P=0.15$) [31[■]].

One study reported that OIT with just 3 ml of cow's milk every 5 days was adequate to produce desensitization with minimal adverse events [32]. Furthermore, a study in 5–18-year-olds who underwent OIT with microwave-heated cow's milk demonstrated that 45% of participants achieved desensitization, whereas 26% achieved 2-week sustained unresponsiveness at 1 year. Desensitization and sustained unresponsiveness remained significantly higher for individuals treated with OIT for 2 years [33]. At approximately 2 years follow-up of 197 patients given OIT, 92.3% were consuming milk protein regularly, 51% experiencing adverse events and 6.7% required epinephrine. In this study, adverse events decreased over time, and expression of CD63 and CD203c, indicators of basophil activation, were significantly lower after 24 months [34]. Another study found that 14/24 children continued to use milk (>200 ml) daily 7 years after beginning OIT, whereas high baseline serum-specific IgE predicted nonuse of milk 7 years later [35].

OIT has also shown promise with inflammatory bowel disease. T-helper type 2 (Th2) polarization and fewer regulatory B cells were found in those with ulcerative colitis along with food allergy. Eighty of these individuals were randomized into OIT alone, probiotic alone, OIT with probiotic or placebo. Only those treated with both OIT and probiotic significantly reduced their ulcerative colitis symptoms and medications while correcting Th2 polarization [36]. This illustrates the close relationship between the immune system and the microbiome.

The Food Allergy Quality of Life Questionnaire-Parental Form was administered to parents 1 week after their children began OIT. A low number of tolerated doses during induction in children aged 6–12 years, but not preschoolers, as well as pre-OIT emergency room referrals, were both significantly associated with lower scores [37]. Another study with milk OIT found that 91% were satisfied with the treatment, and 88% felt that it improved their quality of life, though those with more adverse events reported lower satisfaction [34].

Sublingual immunotherapy

The WHO recognized SLIT as an alternative to subcutaneous immunotherapy (SCIT) in 1998 [38]. SLIT, which uses dissolvable tablets or liquid allergen extracts placed daily under the tongue, is widely used in Europe and the United States [39]. Allergenic proteins persist in the sublingual mucosa for up to 20 h, being taken up by oral Langerhans cells before migrating to regional lymph nodes [40,41]. Gradual absorption makes home SLIT use well tolerated. Unfortunately, manufacturer data indicate that only 13% of SLIT users completed the recommended 3 years of treatment [42]. The U.S. Food and Drug Administration Immunotherapy recently approved allergy immunotherapy tablets (AIT) for grass and ragweed allergies, but SLIT for food allergy remains unapproved given lack of phase III data [43,44]. Ongoing challenges with SLIT using liquid drops include the out-of-pocket expense, lack of standard dosing and the need for personalized formulations to be made for each individual.

Profilin is a protein that induces symptoms in some individuals with plant-derived food allergy. Ten months after seven individuals underwent profilin SLIT, they all demonstrated tolerance to some previously allergenic foods, with no severe adverse event reported [45[■]].

In a recent study of 33 individuals undergoing peanut SLIT, 30% passed a double-blind, placebo-controlled food challenge (DBPCFC) of 2500 mg at 12 months. The desensitized group was found to

have significantly lower baseline levels of peanut-specific IgE, Ara h 2 and Ara h 3 [46]. A recent RDBPCT compared SLIT + placebo OIT with OIT + placebo SLIT. Twelve-month challenge thresholds were significantly greater for the OIT group (141 vs. 22-fold) but OIT had significantly more adverse events including one systemic reaction [47[¶]].

SLIT has been found to positively affect quality of life. A recent study using the SF-12 survey to measure quality of life in 201 pediatric patients treated with SLIT tablets found that scores were comparable with the general population [48]. Another survey asked 228 adults to rank SCIT, SLIT with liquid extracts, AIT and oral mucosal IT (OMIT, using a toothpaste delivery system) in order of preference for use against respiratory allergies. SLIT was ranked significantly higher than other therapies overall with no difference between first-choice rankings of SLIT, AIT and OMIT. However, SLIT, AIT and OMIT were all favored over SCIT. Convenience was cited in 63% of comments explaining the reasons behind their delivery method preference [49[¶]].

Epicutaneous immunotherapy

Epicutaneous immunotherapy (EPIT) is a needle-free method of delivering allergenic proteins to immune competent cells without entry into the vasculature, thereby limiting systemic adverse events [50]. One delivery method of EPIT is by tape stripping skin that allows deeper penetration of allergenic particles through the stratum corneum to reach Langerhans cells [51,52]. Another delivery method is Viaskin, an adhesive polyethylene membrane with allergenic particles that disrupts the stratum corneum by creating a high humidity chamber [53].

Mice sensitized to OVA given OVA-Viaskin patches have shown sustained protection against anaphylaxis triggered by oral allergen challenge. Impaired generation of regulatory T cells (Treg) in mesenteric lymph nodes was corrected with EPIT by production of gastrointestinal homing Latency-associated peptide (LAP)+ Foxp3-Treg-cells that suppress mast cell activation. OIT was less effective at producing sustained unresponsiveness, which was ascribed to oral antigens inhibiting appropriate Treg production, possibly due to mast cell activation in sensitized mice [54].

Another Viaskin sponsored mouse study of EPIT, OIT and SLIT found all three effectively desensitize peanut-sensitized mice compared with placebo by inducing different subsets of Treg-cells. Foxp3+ Cytotoxic T-lymphocyte antigen (CTLA)-4-dependent Treg-cells were induced most by EPIT, whereas LAP+ Treg-cells were induced by both EPIT and OIT.

OIT induced both CTLA-4+ and IL-10+ Treg-cells, whereas SLIT induced strictly IL-10-dependent cells. Interestingly, EPIT-induced Treg-cells remained effective 8 weeks after treatment ended, whereas OIT and SLIT-induced Tregs lost their suppressive properties [55[¶]].

In humans, 24-month data from a recent 171 participant Viaskin Peanut trial found 53.6% of children and 50% overall responded, defined by tolerating a 10-fold dose increase or at least 1000mg of peanut protein on DBPCFC, at 12 months, whereas 80.0% of children and 69.7% of participants overall responded at 24 months. Cumulative reactive doses in children increased by nearly twice as much, and decreases in specific IgE were larger at 24 months (−38%) than at 18 months (−9%). There were no serious adverse events, and adherence to the medication was on average 94% [56,57^{¶¶}]. Another multicenter RDBPCT of 74 participants found Viaskin Peanut 250 µg significantly increased the amount of peanut protein in challenge doses (48% success), whereas Viaskin 100 µg and placebo did not. Success in ages 4–11 years was 62% for Viaskin 250 vs. 14% for both doses in those over age 11 years. Local minor adverse events were common (~80%) in the experimental groups but none required epinephrine [58]. The ongoing MILES study of Viaskin Milk in 2–17-year-old individuals has reported preliminary data on the incidence of itching (83.3%), redness (83.3%) and swelling (72.2%). However, all 18 patients remain in the study, and no severe adverse events have yet occurred [59].

ALLERGEN MODIFICATIONS

Immunomodulatory adjuvants are designed to alter the immunogenicity of specific allergens without being pharmacologically active themselves [60]. They have been used for many years in vaccines, and more recently for airborne allergen immunotherapy, but new uses in the area of food immunotherapy are now being investigated [61]. Poly(lactic-co-glycolic acid) nanoparticles coated with CpG, a short, single-stranded DNA molecule, enhanced the response to peanut OIT in the mouse model [62[¶]]. This preclinical investigation demonstrated a significant increase in IgG₂a levels as well as a decrease in IgE/IgG₁ levels and Th2 cytokines along with protection against anaphylaxis after oral challenge. However, adjuvants may also be used to decrease the immunogenicity of an allergen. An in-vitro study by Plundrich *et al.* [63^{¶¶}] demonstrated that complexes of peanut protein with polyphenols, which are found in foods such as cranberry and green tea, were more rapidly hydrolyzed in the presence of

pepsin, possibly reducing the gastrointestinal side effects seen with OIT.

Peptide immunotherapy (PIT) is based on the standardized production of short, soluble synthetic peptides containing the T-cell epitopes of allergens [64]. These peptides can induce desensitization, but lack the sequences necessary to cross-link IgE on mast cells and basophils, thus potentially decreasing the risk of anaphylaxis [65]. Recently, B-cell epitope-based vaccines have demonstrated an even more favorable side effect profile, compared with T-cell epitopes, but their investigation so far has been limited to airborne allergens [66]. PIT has been used for desensitization to such allergens as cat dander, dust mites, grass pollen and bee venom, but its potential benefits for SIT in food allergy are beginning to be explored [67,68].

Ueno *et al.* [69] determined that by varying the activity of trypsin and chymotrypsin, a hypoallergenic β -lactoglobulin with reduced IgG and IgE antigenicity and maintained T-cell epitopes could be used during OIT for cow's milk allergy. A mixture of six major T-cell epitopes to Met e 1 (shrimp tropomyosin and shellfish panallergen) were found to significantly decrease allergic and systemic symptoms while reducing the Th2-associated antibody and cytokine responses in the mouse model. A shift to a balanced Th1/Th2 response, induction of IgG_{2a} antibodies with blocking activities and regulatory Treg responses also occurred [70[■]]. Murine studies on PIT, using T-cell epitopes directed toward egg (ovomucoid) and milk (β -lactoglobulin), have both shown encouraging results, but the number of proteins involved in cow's milk allergy pose a significant challenge in moving this treatment toward clinical practice [71,72]. Pascal *et al.* [73] described four dominant regions of the Ara h 2 protein that induced in-vitro T-cell proliferation and could represent future PIT candidates for peanut allergy.

Recombinant allergens, purified proteins made from allergen-encoded DNA, have been studied in the setting of SIT for airborne allergens, such as birch pollen, but are now being investigated for use in the treatment of food allergies [74,75]. These allergens can be produced in wild-type form, providing constant supply and standardization, or as genetically modified hypoallergens, with disruption of the IgE binding sites to optimize safety and efficacy [76,77]. IgE binding-site mutagenesis has been performed on cloned and expressed Met e 1, which induced an IgG response in the mouse model along with decreased in-vitro IgE-reactivity in shrimp-allergic humans and Met e 1-sensitized mice [78]. Recently, a Good Manufacturing Practice-level recombinant hypoallergenic carp parvalbumin was characterized in the

mouse model, and human studies are currently underway [79[■]].

In the diagnostic area, sensitivity to recombinant peach allergens (rPru p 1 and rPru p 3) has been found to correlate well with clinical tomato allergy, and recombinant Mal d 1 (the birch pollen homolog found in apples) was also found to be useful and well tolerated for sublingual challenge in humans with oral allergy syndrome [80,81[■]]. Recently, a recombinant clone of the major mango allergen, Man i 1, was produced using an *Escherichia coli* expression system for the potential therapeutic use in future human SIT trials [82[■]]. Peanut desensitization has also been attempted using three recombinant peanut protein hypoallergens (rAra h 1, rAra h 2 and rAra h 3) delivered in heat and phenol killed *E. coli*, but this treatment was stopped after a phase 1 trial in humans due to systemic adverse events [83].

CONCLUSION

Advancements in the treatment of food allergies using SIT have been accelerating rapidly over the past several years, largely due to the limited options currently available coupled with the realization that safety and efficacy of SIT are both within reach. SLIT, EPIT and OIT have each demonstrated some degree of efficacy, but many questions concerning safety and the long-term need for maintenance still need to be addressed. The use of immunomodulatory adjuvants will likely be an important component to food SIT, as this mode of therapy moves steadily toward integration into clinical practice.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

W.R.R. is an advisor and stockholder for Allovate Therapeutics. W.D. has no conflicts of interest to report.

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

1. Sicherer SH, Sampson HA. Food Allergy: epidemiology, pathogenesis, diagnosis and treatment. *J Allergy Clin Immunol* 2014; 133:291–307.
2. Branum AM, Lukacs SL. Food allergy among children in the United States. *Pediatrics* 2009; 124:1549–1555.
3. Turnbull J, Adamsu H, Gerard D. Review article: the diagnosis and management of food allergy and food intolerances. *Aliment Pharmacol Ther* 2015; 41:3–25.

4. Herbert L, Shemesh E, Bender B. Clinical management of psychosocial concerns related to food allergy. *J Allergy Clin Immunol Pract* 2016; 4: 205–213.
5. Lee LA, Burks AW. Food allergies: prevalence, molecular characterizations, and treatment/prevention strategies. *Annu Rev Nutr* 2006; 26:539–565.
6. Skolnick HS, Conover-Walker MK, Koerner CB, *et al*. The natural history of peanut allergy. *J Allergy Clin Immunol* 2001; 107:367–374.
7. Yu JW, Kogan R, Verreault N, *et al*. Accidental ingestions in children with peanut allergy. *J Allergy Clin Immunol* 2006; 118:466–472.
8. Groetch M, Nowak-Węgrzyn A. Practical approach to nutrition and dietary intervention in pediatric food allergy. *Pediatr Allergy Immunol* 2013; 24:212–221.
9. Clark S, Espinola J, Rudders SA, *et al*. Frequency of U.S. emergency department visits for food-related acute allergic reactions. *J Allergy Clin Immunol* 2011; 127:682–683.
10. Canonica GW, Bousquet J, Casale T, *et al*. Sub-lingual immunotherapy: World Allergy Organization position paper 2009. *Allergy* 2009; 64 (Suppl 91):1–59.
11. Brehler R, Klimek L, Kopp MV, *et al*. Specific immunotherapy – indications and mode of action. *Dtsch Arztebl Int* 2013; 110:148–158.
12. Mempel M, Rakoski J, Ring J, *et al*. Severe anaphylaxis to kiwi fruit: immunologic changes related to successful sublingual allergen immunotherapy. *J Allergy Clin Immunol* 2003; 111:1406–1409.
13. Enrique E, Pineda F, Malek T, *et al*. Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. *J Allergy Clin Immunol* 2005; 116:1073–1079.
14. de Boissieu D, Dupont C. Sublingual immunotherapy for cow's milk protein allergy: a preliminary report. *Allergy* 2006; 61:1238–1239.
15. Fernandez-Rivas M, Garrido Fernandez S, Nadal JA, *et al*. Randomized double-blind, placebo-controlled trial of sublingual immunotherapy with a Pru p 3 quantified peach extract. *Allergy* 2009; 64:876–883.
16. Kim EH, Bird JA, Kulis M, *et al*. Sublingual immunotherapy for peanut allergy: clinical and immunology evidence of desensitization. *J Allergy Clin Immunol* 2011; 127:640–646.
17. Fleischer DM, Burks AW, Vickery BP, *et al*. Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial. *J Allergy Clin Immunol* 2013; 131:119–127.
18. Narisety S, Frischmeyer-Guerrero PA, Keet CA, *et al*. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. *J Allergy Clin Immunol* 2015; 135:1275–1282.
19. Burks AW, Wood RA, Jones SM, *et al*. Sublingual immunotherapy for peanut allergy: long-term follow-up of a randomized multicenter trial. *J Allergy Clin Immunol* 2015; 135:1240–1248.
20. Anagnostou K, Clark A. Oral immunotherapy for peanut allergy. *Annu Rev Med* 2015; 67:3.1–3.11.
21. Bravin K, Luyt D. Home-based oral immunotherapy with a baked egg protocol. *J Investig Allergol Clin Immunol* 2016; 26:61–63.
22. Giavi S, Vissers YM, Muraro A, *et al*. Oral immunotherapy with low allergenic hydrolysed egg in egg allergic children. *Allergy* 2016; 71:1575–1584.
23. Gamboa PM, Garcia-Irigoien G, Gonzalez C, *et al*. Is the quantification of antigen-specific basophil activation a useful tool for monitoring oral tolerance induction in children with egg allergy? *J Investig Allergol Clin Immunol* 2016; 26:25–30.
24. Jones SM, Burks AW, Keet C, *et al*. Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy. *J Allergy Clin Immunol* 2016; 137:1117–1127.e1–10. This study is the first multicenter oral immunotherapy (OIT) study to comprehensively survey consumption and symptoms for up to 4 years of treatment and demonstrates that long-term OIT improves sustained unresponsiveness compared with placebo.
25. Wright BL, Kulis M, Orgel KA, *et al*. Component-resolved analysis of IgA, IgE, and IgG4 during egg OIT identifies markers associated with sustained unresponsiveness. *Allergy* 2016; 71:1552–1560.
26. Sugimoto M, Kamemura N, Nagao M, *et al*. Differential response in allergen-specific IgE, IgGs, and IgA levels for predicting outcome of oral immunotherapy. *Pediatr Allergy Immunol* 2016; 27:276–282.
27. Vickery BP, Berglund JP, Burk CM, *et al*. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. *J Allergy Clin Immunol* 2017; 139:173–181.e8.
- First peanut OIT study targeting children younger than 3 years of age.
28. Echeverria-zudaire LA, Fernández-fernández S, Rayo-fernández A, *et al*. Primary eosinophilic gastrointestinal disorders in children who have received food oral immunotherapy. *Allergol Immunopathol (Madr)* 2016; 44:531–536.
29. Pajno GB, Caminiti L, Chiera F, *et al*. Safety profile of oral immunotherapy with cow's milk and hen egg: a 10-year experience in controlled trials. *Allergy Asthma Proc* 2016; 37:400–403.
30. Wood RA, Kim JS, Lindblad R, *et al*. A randomized, double-blind, placebo-controlled study of omalizumab combined with oral immunotherapy for the treatment of cow's milk allergy. *J Allergy Clin Immunol* 2016; 137:1103–1110.e1–11.
- First double-blind, placebo-controlled study of omalizumab in patients with severe persistent milk allergy.
31. Macginnitie AJ, Rachid R, Gragg H, *et al*. Omalizumab facilitates rapid oral desensitization for peanut allergy. *J Allergy Clin Immunol* 2016. [Epub ahead of print]
- First placebo-controlled trial of omalizumab with peanut OIT.
32. Yanagida N, Sato S, Asaumi T, *et al*. A single-center, case-control study of low-dose-induction oral immunotherapy with cow's milk. *Int Arch Allergy Immunol* 2015; 168:131–137.
33. Takahashi M, Taniuchi S, Soejima K, *et al*. Two-weeks-sustained unresponsiveness by oral immunotherapy using microwave heated cow's milk for children with cow's milk allergy. *Allergy Asthma Clin Immunol* 2016; 12:44.
34. Elizur A, Appel MY, Goldberg MR, *et al*. Clinical and laboratory 2-year outcome of oral immunotherapy in patients with cow's milk allergy. *Allergy* 2016; 71:275–278.
35. Paassilta M, Salmivesi S, Mäki T, *et al*. Children who were treated with oral immunotherapy for cows' milk allergy showed long-term desensitisation seven years later. *Acta Paediatr* 2016; 105:215–219.
36. Bin L, Yang F, Lu D, *et al*. Specific immunotherapy plus *Clostridium butyricum* alleviates ulcerative colitis in patients with food allergy. *Sci Rep* 2016; 6:25587.
37. Epstein rigbi N, Katz Y, Goldberg MR, *et al*. Patient quality of life following induction of oral immunotherapy for food allergy. *Pediatr Allergy Immunol* 2016; 27:263–268.
38. Bousquet J, Lockey R, Malling HJ, *et al*. Allergen immunotherapy: therapeutic vaccines for allergic disease. World Health Organization American Academy of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol* 1998; 81:401–405.
39. Linkov G, Toskala E. Sublingual immunotherapy: what we can learn from the European experience. *Curr Opin Otolaryngol Head Neck Surg* 2014; 22:208–210.
40. Bagnasco M, Mariani G, Passalacqua G, *et al*. Absorption and distribution kinetics of the major Parietaria Judaica allergen (Par j1) administered by noninjectable routes in healthy human beings. *J Allergy Clin Immunol* 1997; 100:122–129.
41. Scadding G, Durham S. Mechanisms of sublingual immunotherapy. *J Asthma* 2009; 46:322–334.
42. Incorvaia C, Mauro M, Leo G, *et al*. Adherence to sublingual immunotherapy. *Curr Allergy Asthma Rep* 2016; 16:12.
43. Epstein TG, Calabria C, Cox L, *et al*. Current evidence on safety and practical considerations for administration of sublingual allergen immunotherapy (SLIT) in the United States. *J Allergy Clin Immunol Pract* 2017; 5:34–40.e2.
44. Kobernick AK, Burks AW. Active treatment for food allergy. *Allergol Int* 2016; 65:388–395.
45. Nucera E, Aруanno A, Rizzi A, *et al*. Profilin desensitization: a case series. *Int J Immunopathol Pharmacol* 2016; 29:529–536.
- Largest case series of profilin specific immunotherapy (SIT) for food allergy.
46. Burk CM, Kulis M, Leung N, *et al*. Utility of component analyses in subjects undergoing sublingual immunotherapy for peanut allergy. *Clin Exp Allergy* 2016; 46:347–353.
47. Narisety SD, Frischmeyer-guerrero PA, Keet CA, *et al*. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. *J Allergy Clin Immunol* 2015; 135:1275–1282.e1–6.
- First double-blind, placebo controlled trial to compare the safety and efficacy of oral and sublingual immunotherapy for food allergy.
48. Lemberg ML, Eberle P, Shah-hosseini K. Importance of quality of life for adherence to sublingual immunotherapy. *Biomed Res Int* 2016; 2016: 5186765.
49. Chester JG, Bremberg MG, Reisacher WR. Patient preferences for route of allergy immunotherapy: a comparison of four delivery methods. *Int Forum Allergy Rhinol* 2016; 6:454–459.
- First study of patient preferences for different methods of SIT.
50. Senti G, Von moos S, Kündig TM. Epicutaneous immunotherapy for aero-allergen and food allergy. *Curr Treat Options Allergy* 2014; 1:68–78.
51. Dickel H, Goulioumis A, Gambichler T, *et al*. Standardized tape stripping: a practical and reproducible protocol to uniformly reduce the stratum corneum. *Skin Pharmacol Physiol* 2010; 23:239–265.
52. Swamy M, Jamora C, Havran W, *et al*. Epithelial decision makers: in search of the 'epimicrobiome'. *Nat Immunol* 2010; 11:656–665.
53. Mondoulet L, Dioszeghy V, Ligouis M, *et al*. Epicutaneous immunotherapy on intact skin using a new delivery system in a murine model of allergy. *Clin Exp Allergy* 2010; 40:659–667.
54. Tordesillas L, Mondoulet L, Blazquez AB, *et al*. Epicutaneous immunotherapy induces gastrointestinal LAP(+) regulatory T cells and prevents food-induced anaphylaxis. *J Allergy Clin Immunol* 2017; 139:189–201.e4.
55. Dioszeghy V, Mondoulet L, Puteaux E, *et al*. Differences in phenotype, homing properties and suppressive activities of regulatory T cells induced by epicutaneous, oral or sublingual immunotherapy in mice sensitized to peanut. *Cell Mol Immunol* 2016. [Epub ahead of print]
- First direct comparison of sublingual immunotherapy, OIT and epicutaneous immunotherapy (EPIT) regulatory T-cell properties for peanut allergy.
56. Sampson HA, Agbotounou W, Thébault C, *et al*. Epicutaneous immunotherapy (EPIT) is effective and safe to treat peanut allergy: a multinational double-blind placebo-controlled randomized phase IIb trial. *J Allergy Clin Immunol* 2015; 135:AB390. [abstract]

57. Sampson HA, Agbotounou W, Thébault C, *et al.* Enhanced efficacy and confirmed safety of a two-year epicutaneous immunotherapy (EPIT) treatment of peanut allergy with Viaskin[®]. Peanut: the continuation of the viques phase IIb randomized controlled trial (RCT). *J Allergy Clin Immunol* 2016; 137:AB408–AB1408.
This study demonstrates that epicutaneous immunotherapy is more effective in young children and with longer duration of treatment.
58. Jones SM, Sicherer SH, Burks AW, *et al.* Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. *J Allergy Clin Immunol* 2016. [Epub ahead of print]
59. Rutault K, Agbotounou W, Peillon A, *et al.* Safety of viaskin milk epicutaneous immunotherapy (EPIT) in IgE-mediated cow's milk allergy (CMA) in children (MILES Study). *J Allergy Clin Immunol* 2016; 137:AB132.
60. Pfaar O, Cazan D, Klimek L, *et al.* Adjuvants for immunotherapy. *Allergy Clin Immunol* 2012; 12:648–657.
61. Exley C. Aluminum adjuvants and adverse events in sub-cutaneous allergy immunotherapy. *Allergy Asthma Clin Immunol* 2014; 10:4.
62. Srivastava KD, Siefert A, Fahmy TM, *et al.* Investigation of peanut oral immunotherapy with CpG/peanut nanoparticles in a murine model of peanut allergy. *J Allergy Clin Immunol* 2016; 138:536–543.e4.
This is the first report to describe therapeutic application of nanoparticles in food allergy.
63. Plundrich NJ, White BL, Dean LL, *et al.* Stability and immunogenicity of hypoallergenic peanut protein-polyphenol complexes during *in vitro* pepsin digestion. *Food Funct* 2015; 6:2145–2154.
Immunotherapy with peanut protein–cranberry–green tea polyphenol complexes is less immunogenic once digested by pepsin, suggesting less immunoreactivity when passing through digestive tract.
64. Moldaver D, Larche M. Immunotherapy with peptides. *Allergy* 2011; 66:784–791.
65. Tanabe S. Epitope peptide and immunotherapy. *Curr Protein Pept Sci* 2007; 8:109–118.
66. Valenta R, Campana R, Focke-Tejkl M, *et al.* Vaccine development for allergen-specific immunotherapy based on recombinant allergens and synthetic allergen peptides: lessons from the past and novel mechanisms of action for the future. *J Allergy Clin Immunol* 2016; 137:351–357.
67. Gupta K, Kumar S, Das M, *et al.* Peptide based immunotherapy: a pivotal tool for allergy treatment. *Int Immunopharmacol* 2014; 19:391–398.
68. Couroux P, Patel D, Armstrong K, *et al.* Fel d 1-derived synthetic peptide immuno-regulatory epitopes show a long-term treatment effect in cat allergic subjects. *Clin Exp Allergy* 2015; 45:974–981.
69. Ueno HM, Kato T, Ohnishi H, *et al.* T-cell epitope-containing hypoallergenic β -lactoglobulin for oral immunotherapy in milk allergy. *Pediatr Allergy Immunol* 2016; 0:1–7.
70. Wai CY, Leung NY, Leung PS, *et al.* T cell epitope immunotherapy ameliorates allergic responses in a murine model of shrimp allergy. *Clin Exp Allergy* 2016; 46:491–503.
First peptide-based immunotherapy to effectively reduce allergic response to shrimp tropomyosin. These data suggest that a safer form of subcutaneous immunotherapy for food allergies could be developed in the future.
71. Rupa P, Mine Y. Oral immunotherapy with immunodominant T-cell epitope peptides alleviates allergic reactions in a Balb/c mouse model of egg allergy. *Allergy* 2012; 67:74–82.
72. Meulenbroek LAPM, van Esch BCAM, Hofman GA, *et al.* Oral treatment of β -lactoglobulin peptides prevents clinical symptoms in a mouse model for cow's milk allergy. *Pediatr Allergy Immunol* 2013; 24:656–664.
73. Pascal M, Konstantinou GN, Masilamani M, *et al.* *In silico* prediction of Ara h 2 T cell epitopes in peanut-allergic children. *Clin Exp Allergy* 2013; 43:116–127.
74. Valenta R, Ferreira F, Focke-Tejkl M, *et al.* From allergen genes to allergen vaccines. *Annu Rev Immunol* 2010; 28:211–241.
75. Buonomo A, Nucera E, Schiavino D. Doctor, can I desensitize my food-allergic child using directly the allergenic molecules? *Curr Opin Allergy Clin Immunol* 2016; 16:278–283.
76. Valenta R, Niespöndziana K, Focke-Tejkl M, *et al.* Recombinant allergens: what does the future hold? *J Allergy Clin Immunol* 2011; 127:860–864.
77. Marsh DG, Lichtenstein LM, Campbell DH. Studies on 'allergoids' prepared from naturally occurring allergens. I. Assay of allergenicity and antigenicity of formalized rye group I component. *Immunology* 1970; 18:705–722.
78. Wai CYY, Leung NYH, Ho MHK, *et al.* Immunization with hypoallergens of shrimp allergen tropomyosin inhibits shrimp tropomyosin specific IgE reactivity. *PLoS One* 2014; 9:e111649.
79. Zuidmeer-Jongejan L, Huber H, Swoboda I, *et al.* Development of a hypoallergenic recombinant parvalbumin for first-in-man subcutaneous immunotherapy of fish allergy. *Int Arch Allergy Immunol* 2015; 166:41–51.
First recombinant SIT for fish allergy, showing hypoallergenicity with retained immunogenicity. Currently in randomized, double-blind, placebo controlled trial.
80. Mascheri A, Farioli L, Pravettoni V, *et al.* Hypersensitivity to tomato (*Lycopersicon esculentum*) in peach-allergic patients: rPrup 3 and rPrup 1 are predictive of symptom severity. *J Investig Allergol Clin Immunol* 2015; 25:183–189.
81. Kinaciyan T, Nagi B, Faustmann S, *et al.* Recombinant Mal d 1 facilitates sublingual challenge tests of birch pollen-allergic patients with apple allergy. *Allergy* 2016; 71:272–274.
First recombinant allergen capable of producing standardized sublingual challenges for food allergies.
82. Tsai WC, Wu TC, Chiang BL, *et al.* Cloning, expression, and purification of recombinant major mango allergen Man I 1 in *Escherichia coli*. *Protein Expr Purif* 2017; 130:35–43.
First identification and recombinant production of mango allergen, which may be used for SIT in the future.
83. Wood RA, Sicherer SH, Burks AW, *et al.* A phase 1 study of heat/phenol killed, *E. coli*-encapsulated, recombinant modified peanut proteins Ara h 1, Ara h 2, and Ara h 3 (EMP-123) for the treatment of peanut allergy. *Allergy* 2013; 68:803–808.