

Adjuvant Therapies in Food Immunotherapy



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KEYWORDS

- Food allergy • Adjuvants • Probiotics • Bacterial adjuvants • Omalizumab
- Interferon gamma

KEY POINTS

- Although oral immunotherapy (OIT) for food allergy is effective at inducing desensitization, it seems to have a limited ability to induce tolerance and is associated with high rates of adverse reactions.
- Use of an adjuvant with food immunotherapy may reduce adverse reactions and/or enhance tolerance induction (also referred to as sustained unresponsiveness).
- Adjuvants like anti-immunoglobulin E monoclonal antibody and interferon-gamma improve tolerability of OIT by reducing adverse reactions, whereas immune response modifiers such as probiotic bacteria or bacterial components may enhance OIT-induced sustained unresponsiveness.

INTRODUCTION

Currently, food allergy management relies on allergen avoidance and emergency treatment of allergic reactions. Although most reactions are managed effectively, fatalities can rarely occur, with an estimated incidence of approximately 3 per million person-years for children aged 0 to 19 years.¹ The constant vigilance required to maintain food allergen avoidance and the potential for life-threatening reactions result in a reduced quality of life.² Finding a curative treatment is imperative to improve quality of life and prevent food allergy-related deaths.

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Allergen immunotherapy has been successfully applied to treat allergic rhinitis, asthma, and venom anaphylaxis. However, an attempt to use subcutaneous immunotherapy for treatment of peanut allergy in the 1990s resulted in high rates of systemic reactions and the approach was abandoned.³ Subsequently, alternative routes of delivery, such as oral or sublingual immunotherapy (See Christopher P. Parrish and colleagues' article, "[Interventional Therapies for the Treatment of Food Allergy](#)," in this issue.), use of modified allergens (See Melissa L. Robinson and Bruce J. Lanser's article, "[The Role of Baked Egg and Milk in the Diets of Allergic Children](#)," in this issue.), and cotreatment with adjuvants to reduce adverse reactions or improve efficacy have been investigated with varying results. This article discusses the use of adjuvants to improve the safety and/or effectiveness of food immunotherapy.

IDENTIFYING AN OPTIMAL OUTCOME: DESENSITIZATION VERSUS SUSTAINED UNRESPONSIVENESS

Potential food allergy treatments can offer 2 possible outcomes: desensitization or tolerance. Desensitization is defined as an increase in the threshold for reaction and requires continued regular allergen exposure.⁴ This clinical unresponsiveness is temporary and lasts only while allergen ingestion is maintained. Tolerance is the state of prolonged immune unresponsiveness that persists after withdrawal of the allergen for a period of several weeks or months. There is currently no consensus on the duration of secondary allergen elimination required to accurately identify tolerance. Consequently, the term *sustained unresponsiveness* (SU) has been introduced to describe the state of unresponsiveness after a period of secondary avoidance following food immunotherapy⁵ and is the preferred term when describing food immunotherapy trial outcomes.

There is a lack of consensus regarding the ultimate goal of immunotherapy. Desensitization offers the individual protection against accidental ingestion to limited amounts of food allergen, however, they remain allergic to the food allergen; hence, reactions can and do occur, including to previously tolerated doses. In the case of oral immunotherapy (OIT), approximately 65%-75% of desensitized individuals reported frequent and often severe allergic reactions to previously tolerated doses.^{6,7} Furthermore, approximately 50% of desensitized individuals were unable to continue regular allergen intake because of adverse reactions.⁷ Another limitation of desensitization as a treatment outcome is that protection can be lost over time.⁷ It is, therefore, uncertain whether desensitization offers an improvement for individuals with food allergy compared with allergen avoidance. Achieving tolerance or SU would seem to be the preferred treatment outcome following food immunotherapy, as this would theoretically allow consumption of unrestricted amounts of the allergenic food ad libitum without a reaction.

LIMITATIONS OF ORAL IMMUNOTHERAPY AS A POTENTIAL TREATMENT OF FOOD ALLERGY

Cumulative evidence confirms that OIT is effective at inducing desensitization in most peanut, egg, and milk allergic patients^{8,9}; however, SU is only achieved in about a third of patients following peanut, egg, or milk OIT.⁸ Furthermore, OIT-induced SU seems to be short-lived, with 50% of subjects who achieved SU at 3 months after peanut OIT losing SU by 6 months after treatment.^{10,11} Suppression of the allergen-specific immunologic response similarly seems to be transient.¹²

Adverse events with OIT are frequent. Reactions requiring adrenaline occur more frequently than with dietary avoidance.⁹ Up to 20% of participants fail to reach the

target maintenance OIT dose because of significant gastrointestinal symptoms or anaphylaxis^{13,14}; 10% to 30% withdraw from OIT trials because of adverse events,⁴ and eosinophilic esophagitis has been reported in up to 10% to 15%.^{15,16} Most studies excluded patients with severe food-induced anaphylaxis, so reaction rates may be even higher in unselected food-allergic populations. The limited ability of OIT to induce SU and high rates of adverse reactions highlight the need for novel strategies to enhance tolerance induction and reduce adverse reactions with OIT.

ADJUVANT THERAPIES

One approach to reduce OIT-associated adverse reactions and/or enhance the tolerogenic effects of OIT is the use of an adjuvant together with food immunotherapy. Adjuvants may be selected for their ability to suppress the acute allergic reaction and/or modulate the underlying allergic immune response, respectively.

Inhibition of the Immunoglobulin E–Mediated Allergic Response

Anti-immunoglobulin E monoclonal antibody

Anti-immunoglobulin E (IgE) monoclonal antibody (mAb) was first introduced as an adjunctive therapy to reduce OIT-related allergic reactions. Omalizumab is a humanized recombinant mAb that binds to the CH₃ region of IgE and prevents binding of IgE to FcεRI and FcεRII receptors on mast cells and basophils, thereby preventing mast cell and basophil activation. Omalizumab also downregulates the expression of IgE receptors on mast cells, basophils, and dendritic cells.¹⁷ The addition of omalizumab to immunotherapy in patients with asthma,¹⁸ allergic rhinitis,¹⁹ and venom hypersensitivity²⁰ reduced the number of adverse events, allowing more rapid dose escalation and higher maintenance doses. These findings provided the rationale for using anti-IgE mAbs with immunotherapy in food allergy.

Both TNX-901, another anti-IgE mAb,²¹ and omalizumab^{22,23} have been shown to increase the threshold of reactivity in oral food challenges. Omalizumab was first used in combination with OIT in children with milk allergy.²⁴ Eleven children received omalizumab every 2 to 4 weeks for 9 weeks before starting oral cow's milk desensitization. Omalizumab was discontinued after 16 weeks, and daily oral milk ingestion was continued at home. Nine of the 11 patients passed a double-blind placebo-controlled food challenge (DBPCFC) assessing for desensitization at week 25. In another study, omalizumab was administered for 12 weeks before peanut OIT.²⁵ Twelve of 13 patients passed a DBPCFC after 32 weeks of OIT, confirming successful desensitization. Although most patients had mild or no reactions, 2 required adrenaline at home for reactions associated with exercise, infection, or nonsteroidal antiinflammatory drug use during the maintenance phase (after omalizumab was discontinued).

Subsequent reports support the effectiveness of omalizumab in facilitating faster attainment of higher maintenance OIT doses with fewer dose-related symptoms (Table 1^{24–29}). However, Lafuente and colleagues²⁹ described 3 children who were successfully desensitized with omalizumab-assisted egg OIT and later experienced a recurrence of symptoms 3 to 4 months after stopping omalizumab while still continuing OIT. All 3 subjects presented with gastrointestinal symptoms that resolved once omalizumab was restarted. Therefore, the protective benefit offered by omalizumab may be lost as antibody titers decrease and a longer treatment duration may be required for highly reactive individuals to complete a standard OIT schedule. Patients who have received omalizumab-assisted OIT should be monitored to ensure continued patient safety when the effect of omalizumab has waned.

Table 1
Omalizumab

Author	Study Design Sample Size	Allergen	Duration	Outcome
Nadeau et al, ²⁴ 2011	Phase I n = 11	Milk	16 wk	9 of 11 subjects desensitized
Schneider et al, ²⁵ 2013	Phase I n = 13	Peanut	20 wk	12 of 13 subjects desensitized
Takahasi et al, ²⁶ 2015	Case report n = 1	Milk	12 mo	Passed open food challenge conducted after 2 wk of allergen avoidance after treatment
Wood et al, ²⁷ 2016	DBPC randomized trial Omalizumab + OIT n = 28; OIT n = 29	Milk	28 mo	Desensitization: omalizumab + OIT 88.9% (24 of 28) vs OIT 71.4% (20 of 29) ($P = .18$) SU: omalizumab + OIT 48.1% (13 of 28) vs OIT 35.7% (10 of 29) ($P = .42$)
Begin et al, ²⁸ 2014	Phase I n = 25	Multiple foods	16 wk	22 of 25 subjects desensitized
Lafuente et al, ²⁹ 2014	Case report n = 3	Egg	4–7 mo	3 of 3 subjects desensitized; developed recurrence of symptoms after stopping omalizumab

Abbreviation: DBPC, double-blind placebo-controlled.

Wood and colleagues²⁷ examined whether adding omalizumab to OIT can increase the rates of OIT-induced desensitization or SU in a double-blind placebo-controlled trial. Fifty-seven subjects with milk allergy were randomized to omalizumab or placebo commenced 4 months before initiation of OIT and discontinued at month 28 when a DBPCFC was performed to assess for desensitization. Those who passed the desensitization DBPCFC continued on OIT for a further 8 weeks, after which OIT was discontinued and a second DBPCFC performed 2 months later to assess for SU. Although omalizumab was associated with fewer adverse reactions to OIT and fewer doses required to achieve the maintenance dose, there was no significant effect on achieving desensitization or 2-month SU.

In summary, omalizumab used as an adjunct to OIT seems to be effective in reducing reactions during OIT dose escalation. However, reactions may resume once omalizumab is discontinued. There is currently no evidence that omalizumab added to OIT can increase the likelihood of OIT-induced desensitization or tolerance. Further studies are required to determine if the initial benefit provided by omalizumab converts to improved long-term outcomes. The high cost of omalizumab is a necessary consideration given that longer periods of maintenance therapy may be required to support highly allergic individuals through a full course of OIT.

Interferon-gamma

The balance of T helper (Th)1 and Th2 responses plays a central role in IgE regulation and the development of allergic disease. Increased production of interferon-gamma (IFN- γ) has been associated with a resolution of food allergy in murine models^{30,31} and patients with cow's milk allergy.³²

Hence, the combined administration of IFN- γ with OIT was evaluated in a small case control study.³³ Twenty-five children with egg, milk, or wheat allergy confirmed by open food challenges were assigned to receive IFN- γ with OIT ($n = 10$), OIT alone ($n = 5$), IFN- γ alone ($n = 5$), or no treatment ($n = 5$). Subcutaneous recombinant IFN- γ (Intermax Gamma) was administered 10 to 20 minutes before each dose of OIT. Open food challenges were performed after completing treatment and 3 months after treatment cessation. All 10 patients who received IFN- γ with OIT successfully achieved a 3-month SU. Dose-related symptoms were mild and delayed in onset, with skin manifestations changing from acute IgE-mediated symptoms to delayed eczematous reactions. None of the subjects who received either IFN- γ alone or OIT alone were desensitized; all OIT participants failed to complete the OIT protocol and withdrew because of frequent and severe reactions. Combined IFN- γ and OIT was associated with increased food-specific IgE, although the skin prick test wheal size decreased. A subsequent study³⁴ demonstrated desensitization with a combination IFN- γ and OIT, although the effect on SU was not assessed (Table 2).

These preliminary results suggest that IFN- γ administered with OIT may support completion of OIT and the development of SU. However, findings should be interpreted with caution given the small sample size. Larger randomized controlled trials are needed to confirm these effects.

Immune Response Modifiers

There has been growing interest in a class of adjuvants known as immune response modifiers (IRMs). IRMs typically signal through pathogen recognition receptors, including Toll-like receptors (TLRs) on dendritic cells (DCs). DCs are professional antigen-presenting cells that link innate and adaptive immunity and play a crucial role in orchestrating the T-cell response. Certain populations of DCs have tolerogenic

Table 2 Interferon gamma				
Author	Study Design Sample Size	Allergen	Duration	Outcome
Noh & Lee, ³³ 2009	Case control IFN- γ + OIT n = 10; OIT n = 5; IFN- γ n = 5; no treatment n = 5	Milk, egg, wheat	Depends on food	Ten of 10 subjects who received IFN- γ + OIT achieved SU. None of the subjects who received OIT alone, IFN- γ alone, or no treatment desensitized or achieved SU.
Noh & Jang, ³⁴ 2014	Case control IFN- γ /dual OIT ^a n = 10; IFN- γ /classic OIT ^b n = 5; OIT n = 5; no treatment n = 5	Milk, egg, wheat, soy	Depends on food	Ten of 10 of subjects who received dual OIT and 5 of 5 subjects who received classic OIT desensitized. None of the subjects who received OIT alone or no treatment desensitized.

^a Dual OIT consists of a dose of interferon gamma with OIT in the morning and a dose of OIT alone in the evening.

^b Classic OIT consists of a single daily dose of interferon gamma with OIT.

capacity and actively promote oral tolerance,^{35,36} through complex mechanisms that likely involve the induction of peripheral Foxp3+ T-regulatory cells.

Toll-like receptor ligands

TLR agonists are more immunogenic than conventional adjuvants and induce long-lasting T-regulatory and Th1 responses resulting in a shift from IgE to IgG production.^{37,38} Their combined administration with immunotherapy has been explored as an approach to enhance the effectiveness of immunotherapy in treatment of airway allergic disease, with the aim of shortening the duration of immunotherapy. Combined administration of monophosphoryl lipid A, an adjuvant derived from bacterial lipopolysaccharide that signals through TLR4, with subcutaneous and sublingual pollen immunotherapy was effective in the treatment of asthma and allergic rhinitis in children and adults^{39–41}; a preseasonal ultrashort course of 4 doses repeated annually for 3 years provided a long-lasting benefit for up to 5 years after stopping treatment.^{42–44} Similar results were reported for CpG-ragweed pollen antigen Amb a1⁴⁵ and CpG-house dust mite⁴⁶ immunotherapy for allergic rhinoconjunctivitis.

Animal studies suggest that TLR-agonist approaches may offer similar benefits in food allergy. TLR agonists induced a shift from Th2 to Th1 responses in murine models of peanut allergy.^{47,48} CpG/peanut-nanoparticles prevented anaphylaxis to oral peanut challenge, reduced Th2 cytokines, and increased IFN- γ levels in peanut-allergic mice.⁴⁹ Further studies in food-allergic patients are warranted.

Modified bacteria expressing allergenic proteins

Bacterial adjuvants have also been explored for enhancing the effectiveness of immunotherapy based on their ability to induce Th1 responses. The concept is to use attenuated bacteria as carriers to deliver engineered recombinant allergens to the host immune system thereby inducing Th1 responses to the expressed allergens. The major peanut allergens (Ara h 1, Ara h 2, Ara h 3) were engineered to disrupt

immunodominant IgE-binding sites, and these engineered recombinant allergens were then expressed by heat-killed *Listeria monocytogenes*⁵⁰ and *Escherichia coli*.⁵¹ The administration of these genetically modified heat-killed organisms to peanut-allergic mice protected mice from anaphylaxis and resulted in a shift to a Th1 response with decreased allergen-specific IgE levels. These preclinical studies led to a phase I trial of heat/phenol killed *E coli* encapsulated recombinant modified peanut proteins Ara h 1, Ara h 2, and Ara h 3 (EMP-123) in human subjects with peanut allergy and healthy controls.⁵² Rectal administration to healthy volunteers showed no adverse effects; however, 5 of 10 peanut-allergic patients failed to complete treatment because of severe adverse reactions, including 2 anaphylactic reactions (Table 3). Post hoc analyses of immune markers showed no changes in total IgE, peanut-specific IgE or peanut-specific IgG4. Further studies evaluating alternate routes of administration are planned.

Bacterial S-layers that make up the outermost layer of many bacteria have strong adjuvant properties,⁵³ making them particularly suitable as antigen carriers in vaccines. Anzengruber and colleagues⁵⁴ recently evaluated the use of *Lactobacillus buchneri* S-layer fused to an Ara h 2-derived peptide as a candidate vaccine for peanut OIT. The fusion protein induced Ara h 2-specific blocking IgG in the rabbit model, suggesting another potential allergen peptide-based bacterial carrier vaccine approach.

Combined administration of probiotic bacteria together with food allergen

Probiotic bacteria are defined as live bacteria that provide a beneficial effect when administered in adequate amounts.⁵⁵ Probiotic bacteria have a long record of safe oral consumption and are generally regarded as safe by the Food and Drug Administration. The most well-characterized probiotic bacteria include species from the *Lactobacilli* and *Bifidobacteria* genera. The only randomized trial evaluating probiotics for the treatment of food allergy compared a mixture of *Lactobacillus* and *Bifidobacteria* species with placebo in infants with cow's milk allergy. No significant difference in the acquisition of tolerance was demonstrated.⁵⁶ Nevertheless, probiotic bacteria have potent immune effects and selected *Lactobacillus* species have been shown to support tolerogenic immune responses, including promoting Th1 cytokine responses with increased production of IFN- γ , T-regulatory responses with increased production of IL-10,^{57,58} and allergen-specific IgA responses.^{59,60} It was, therefore, considered that combined administration of a tolerogenic probiotic together with food OIT may enhance tolerance induction with OIT.

Tang and colleagues⁶¹ performed a double-blind placebo-controlled randomized trial of probiotic *Lactobacillus rhamnosus* CGMCC 1.3724 and peanut OIT (PPOIT) in 62 children with peanut allergy. Subjects received a fixed dose of probiotic (or placebo) together with peanut OIT (or placebo) once daily for a total of 18 months. SU, determined by DBPCFC conducted 2 to 5 weeks after discontinuation of treatment, was achieved in 82.1% of patients receiving PPOIT compared with 3.6% of those receiving placebo, the highest rate of SU reported for any food immunotherapy treatment evaluated in a randomized controlled study to date. PPOIT also induced high rates of desensitization (90%) and was associated with reduced peanut skin test reactivity, decreased peanut-specific IgE, and increased peanut-specific IgG4 levels. PPOIT was well tolerated with no participants withdrawing because of adverse reactions (6 participants withdrew for reasons unrelated to PPOIT treatment); this is in stark contrast to OIT whereby 10% to 30% of participants withdraw because of adverse reactions. Long-term follow-up of participants 4 years after completing treatment showed long-lasting clinical and immunologic benefit.⁶² PPOIT-treated

Table 3
Bacterial adjuvants

Author	Study Design Sample Size	Adjuvant/Allergen	Duration	Outcome
Wood et al, ⁵² 2013	Phase I Healthy controls n = 5; peanut allergy n = 10	EMP-123 Peanut	13 doses	Safety: 5 of 10 peanut allergic subjects failed to complete treatment because of adverse reactions.
Tang et al, ⁶¹ 2015	DBPC randomized trial PPOIT n = 31; placebo n = 31	<i>Lactobacillus rhamnosus</i> Peanut	18 mo	Desensitization: PPOIT 89.7% (26 of 29) vs placebo 7.1% (2 of 28) ($P < .001$) SU: PPOIT 82.1% (23 of 28) vs placebo 3.6% (1 of 28) ($P < .001$)
Berni Canani et al, ⁶³ 2013	EHF + LGG n = 71; EHF alone n = 55; HRF n = 46; SF n = 55; AAF n = 33	<i>Lactobacillus rhamnosus</i> Cow's milk	12 mo	Tolerance: EHF + LGG 78.9% vs EHF alone 43.6% vs HRF 32.6% vs SF 23.6% vs AAF; EHF + LGG (OR 28.62, 95% CI 8.72–93.93; $P < .001$); EHF (OR 4.41, 95% CI 1.44–13.48; $P = .009$)
Berni Canani et al, ⁶⁴ 2012	EHF + LGG n = 27; EHF n = 28	<i>Lactobacillus rhamnosus</i> Cow's milk	12 mo	Tolerance: EHF + LGG 81.5% (22 of 27) vs EHF 53.6% (15 of 28)

Abbreviations: AAF, amino acid based formula; DBPC, double-blind placebo-controlled; EHF, extensively hydrolyzed cow's milk formula; HRF, hydrolyzed rice formula; LGG, *Lactobacillus rhamnosus*; PPOIT, probiotic and peanut oral immunotherapy; SF, soy formula.

participants were more likely to have continuing peanut intake than placebo participants (66.7% vs 4.2%; absolute difference 62.5, 95% confidence interval [CI] 42.0, 83.0; $P < .01$). Reactions were uncommon in both PPOIT and placebo-treated groups: 4 PPOIT and 6 placebo participants reported allergic reactions to peanut on intentional or accidental peanut intake since stopping the treatment, with no anaphylaxis episodes. PPOIT treatment was also associated with smaller peanut SPT and substantially higher peanut-specific IgG4:IgE ratio (91.4 vs 2.4; $P = .02$) than placebo treatment at 4 years posttreatment. Furthermore, 58.3% (7 of 12) of PPOIT compared with 6.7% (1 of 15) of placebo participants ($P = .03$) had persistent SU (assessed by DBPCFC after 8 weeks of peanut elimination) 4 years after treatment. One of the limitations of this study was the lack of a control group receiving OIT alone (without probiotics), so it is not certain that the addition of probiotic-enhanced tolerance acquisition compared with OIT alone. A larger multicenter randomized controlled trial is currently underway comparing PPOIT, placebo/peanut OIT, and placebo/placebo, which will clarify whether PPOIT is more effective than peanut OIT alone.

Berni Canani and colleagues⁶³ evaluated a similar treatment approach in cow's milk allergy and showed that coadministration of the probiotic *L. rhamnosus* ATCC 53103 (trade name *L. rhamnosus* GG) together with extensively hydrolyzed cow's milk formula (EHF) resulted in a higher rate of tolerance compared to feeding with EHF alone or to complete allergen avoidance. The open controlled study compared the effects of 5 different treatments in 260 infants with cow's milk allergy: EHF ($n = 55$); EHF with *L. rhamnosus* GG ($n = 71$); hydrolyzed rice formula ($n = 46$); soy formula ($n = 55$); and amino acid-based formula ($n = 33$). Although EHF is considered hypoallergenic with most IgE-reactive epitopes removed, they still contain residual cow's milk peptides that could support an immunotherapy effect; hence, the groups receiving EHF could be considered to be on quasi OIT with modified (hydrolyzed) cow's milk allergen. On the other hand, the groups receiving amino acid-based formula, hydrolyzed rice formula, and soy formula could be considered to be maintaining complete allergen avoidance. The rate of tolerance after 12 months was significantly higher in the groups receiving EHF (43.6%) or EHF/*L. rhamnosus* GG (78.9%) compared with the other groups (hydrolyzed rice formula [32.6%], soy formula [23.6%], amino acid based formula [18.2%]). Binary regression analysis revealed that tolerance was significantly more likely in infants receiving EHF (odds ratio [OR] 4.41, 95% CI 1.44–13.48; $P = .009$) or EHF/*L. rhamnosus* GG (OR 28.62, 95% CI 8.72–93.93; $P < .001$). Taken together, the findings of Tang and colleagues and Berni Canani and colleagues provide a compelling argument that combined administration of the probiotic adjuvant *L. rhamnosus* (either CGMCC 1.3724 or ATCC 53103) together with OIT can significantly enhance the likelihood of OIT-induced SU, in the setting of peanut and milk allergy. Further randomized controlled trials are warranted to confirm these findings.

FUTURE CONSIDERATIONS AND SUMMARY

Considering the significant impact of food allergy on individuals and society, finding a therapy that can alter the natural course of disease is a major priority. Although OIT can induce desensitization in a high proportion of treated patients, studies suggest it is less effective at inducing SU. Moreover, OIT is associated with frequent adverse effects. Anti-IgE mAb administered together with OIT improved the tolerability of OIT by reducing adverse reactions and increasing the likelihood for individuals to reach maintenance dosing but failed to influence the acquisition of SU. A small study showed that combined IFN- γ and OIT treatment reduced the rate and severity of OIT reactions and supported the development of SU. Further studies are required to

confirm these findings. Immune-modifying adjuvants that promote TLR responses offer a promising means of enhancing OIT-induced SU. The immune-modifying adjuvant therapies currently under development include genetically engineered bacterial carriers expressing modified food allergens and the coadministration of probiotic bacteria together with OIT. The probiotics *Lactobacillus rhamnosus* CGMCC 1.3724 and ATCC 53103 seem to be particularly effective when combined with OIT, inducing sustained unresponsiveness in a high proportion of allergic subjects with milk or peanut allergy. Future studies investigating the use of bacterial adjuvant/OIT in other food allergy conditions will clarify whether this combination therapy represents a platform approach for inducing SU in any food allergy.

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