

Novel Therapies for Treatment of Food Allergy



Sultan Albuhairei, MD^a, Rima Rachid, MD^{b,*}

KEYWORDS

- Food allergy • Novel therapies • Biologics • Microbiome
- Fecal microbiota transplantation • Omalizumab • Dupilumab

KEY POINTS

- There is an unmet need to evaluate new therapeutic modalities that may decrease the risk of food-induced anaphylaxis and improve patients' quality of life.
- Oral, epicutaneous, and sublingual food immunotherapies have different safety and efficacy profiles, and their long-term outcome and applicability are unclear.
- Food allergy trials are currently evaluating different biologics (given as monotherapy or adjunct to immunotherapy), modified food proteins, DNA vaccines, and fecal microbiota transplantation.

INTRODUCTION

The prevalence of food allergy has significantly increased over time. The Centers of Disease Control and Prevention in the United States reported an increase in food allergy among children from 3.4% in 1997 to 2007 to 5.1% in 2009 to 2011.¹ Large surveys in the United States estimated that at least 4% to 10% of adults (26 million) and 8% of children have food allergy.^{2,3} Standard of care currently consists of food allergen avoidance and keeping rescue medications including epinephrine and antihistamines for emergency use.⁴ Unfortunately, food allergy can affect quality of life of affected patients and their families significantly, and can lead to significant social impact, anxiety, and dietary limitations.⁵

Although there are currently no treatments approved by the Food and Drug Administration (FDA) for food allergy, food immunotherapy via the oral (OIT), epicutaneous (EPIT), and sublingual routes (SLIT) has been evaluated in numerous trials over the

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^a Department of Pediatrics, College of Medicine, Majmaah University, PO Box 66, Majmaah 11952, Saudi Arabia; ^b Division of Immunology, Department of Pediatrics, Boston Children's Hospital, Harvard Medical School, 300 Longwood Avenue, Boston, MA 02115, USA

* Corresponding author.

E-mail address: rima.rachid@childrens.harvard.edu

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past decade.⁶ The success and side effects of these techniques is variable depending on the route, build-up protocol, maintenance dose, or food used. Recently a large study on 496 children who reacted to ≤ 100 mg peanut protein during entry food challenge showed that 67% of participants on AR101 pharmaceutical peanut product tolerated at least 600 mg of peanut protein during exit food challenge compared with 4% on placebo. However, 4.3% of subjects on study drug developed severe allergic reactions compared with 0.8% of placebo.⁷ EPIT on the other side, using Via-skin Peanut, had less efficacy in peanut-allergic children aged 4 to 11 years, as the percentage difference in responders at 12 months with the 250- μ g peanut-patch therapy versus placebo was 21.7%. Systemic side effects were much less frequent compared with peanut OIT and there was no severe anaphylaxis reported.⁸ None of these food immunotherapy approaches are known to lead to a permanent oral tolerance (cure). In clinical trials, the surrogate term for permanent tolerance, sustained unresponsiveness (SU) is used. SU, which is evaluated by successfully passing a food challenge after withholding immunotherapy for a defined period, was observed in only 50% of patients who were on peanut OIT for up to 5 years and interrupted therapy for 4 weeks.⁹ However, SU was reported in only 15% of patients who stopped peanut OIT for 6 months, suggesting that the longer the period of avoidance, the lower SU rate.¹⁰ A recent meta-analysis of 12 peanut OIT trials that included 1041 subjects reported that high-certainty evidence shows that the analyzed peanut OIT regimens considerably increase allergic and anaphylactic reactions compared with avoidance or placebo, despite effectively inducing desensitization.¹¹

There is therefore an unmet need to explore other therapies for food allergy, which may be administered either separately or in combination with food immunotherapy. Fortunately, there are several immunomodulatory candidates that are currently being evaluated or are candidates for investigation. In this review article, the authors discuss some of these novel potential food allergy investigational therapies (Tables 1 and 2).

MECHANISM OF FOOD ALLERGY

Food allergy results from the immunologic loss of tolerance to specific food allergens. The exact mechanism underlying the development of food allergy and the subsequent allergic response remains to be elucidated. The modified hygiene hypothesis stipulates that the Western life style limits the gut microbiome exposure, leading to disruption in the healthy gut microbiota or dysbiosis. Healthy commensal gut bacteria protect the intestinal mucosal barrier and target both innate and adaptive immune response to promote tolerance to food.¹² *Clostridia* colonization of germ-free mice protects from oral allergen sensitization by inducing interleukin (IL)-22+ innate lymphoid cell C type 3 (ILC3) at the intestinal mucosa.¹³ IL-22 promotes mucosal integrity, which prevents leakage of protease-resistant food allergens through the gut mucosal barrier.¹³ In addition, commensal microbiota directly acts on regulatory T (Treg) cells through their toll-like receptors (TLRs) and promotes the development of induced Treg (iTreg) cells. We recently found that commensal bacteria can upregulate the development of RoR γ Treg cells in a Myd88-dependent manner and that RoR γ Treg cells are essential for the development of tolerance.¹⁴ Hence, dysbiosis leads to increased epithelial gut permeability. This in turn results in increased production of epithelial derived cytokines, including IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) with subsequent upregulation of Th2-driven inflammatory response and production of cytokines IL-4, IL-5, and IL-13. This promotes recruitment of mast cells, eosinophils, and basophils and ultimately the formation of allergen-specific immunoglobulin (IgE) antibody.¹⁵ On exposure, the food-specific IgE bound to

Table 1 Investigational therapies for food allergy		
Therapeutic Agents	Clinical Trials in Food Allergy	References or NCT Number
Anti-IgE		
Omalizumab (Anti-IgE mAb)	Monotherapy for peanut allergy	Savage et al, ¹⁸ 2012 Sampson et al, ¹⁹ 2011 Fiocchi et al, ²⁰ 2019 Leung et al, ⁶⁷ 2003
	Adjunct to peanut, milk or multi-food OIT	Nadeau et al, ²¹ 2011 MacGinnitie et al, ²² 2017 Schneider et al, ²³ 2013 Wood et al, ²⁴ 2016 Andorf et al, ²⁵ 2017; Andorf et al, ²⁶ 2018
Anti-IL 4R		
Dupilumab (Anti-IL4-R mAb)	Monotherapy for peanut allergy	Phase II (NCT03793608)
	Adjunct to peanut OIT	Phase II (NCT03682770)
Th1 adjuvants		
Glucopyranosyl lipid A (GLA)	Adjunct to peanut SLIT	Phase I (NCT03463135) (Trial has been terminated prematurely)
Anti-TSLP and IL-33		
Etokimab (anti-IL-33 Ab)	Peanut allergy	Phase II (NCT02920021)
DNA vaccines		
ASP0892 (ARA-LAMP-vax)	Peanut allergy	Phase I (NCT03755713) Phase I (NCT02851277)
Modified food allergen proteins		
Encapsulated, recombinant modified peanut proteins Ara h 1, Ara h 2, and Ara h 3 (EMP-123)	Peanut allergy	Wood et al, ⁵⁹ 2013
HAL-MPE1	Peanut allergy	Phase I (NCT02991885)
Anti- Sialic acid binding immunoglobulin like lectin (Siglec-8) Antibody (AK002)	Eosinophilic gastritis and/or eosinophilic gastroenteritis	Phase II (NCT03496571)
Ibrutinib (Bruton's tyrosine kinase inhibitor)	Peanut allergy	Dispenza et al, ⁶⁸ 2018
Targeting the microbiome		
Probiotics	Cow's milk allergy	Berni Canani et al, ⁶¹ 2012; Berni Canani et al, ⁶⁹ 2017 Hol et al, ⁶² 2008 Zhang et al, ⁶³ 2016
Probiotic with peanut oral immunotherapy	Peanut allergy	Tang et al, ⁶⁴ 2015
Fecal microbiota transplantation (FMT)	Peanut allergy	Phase I (NCT02960074)

Abbreviations: Ig, immunoglobulin; IL, interleukin; LAMP, lysosomal-associated membrane protein; mAb, monoclonal antibody; OIT, oral immunotherapy; SLIT, sublingual immunotherapy; TSLP, thymic stromal lymphopoietin.

Table 2 Investigational therapies for other atopic diseases	
Therapeutic Agents	FDA Approval or Clinical Trial for Asthma, Chronic Urticaria and/or Atopic Dermatitis Therapy
Anti-IgE	
Ligelizumab (Anti-IgE mAb)	Phase IIIb for chronic spontaneous urticaria Phase II for asthma
Anti-IL-5 and Anti-IL-5R	
Mepolizumab (Anti-IL-5 mAb)	FDA approved for asthma treatment (≥ 12 y)
Reslizumab (Anti-IL-5 mAb)	FDA approved for asthma treatment (adults)
Benralizumab (Anti-IL-5-R mAb)	FDA approved for asthma treatment (≥ 12 y)
Anti-IL 13	
Lebrikizumab (Anti-IL-13 mAb)	Phase III for atopic dermatitis, asthma
Tralokinumab (Anti-IL-13 mAb)	Phase III for atopic dermatitis, asthma
Th1 adjuvants	
CpG oligodeoxynucleotides	Phase II for allergic rhinitis
Monophosphoryl Lipid A (MPL)	Phase II for allergic rhinitis
Anti-TSLP and IL-33	
Tezepelumab (anti-TSLP mAb)	Phase II for asthma and atopic dermatitis in adults
Etokimab (anti-IL-33 Ab)	Phase II for atopic dermatitis in adults

Abbreviations: FDA, Food and Drug Administration; Ig, immunoglobulin; IL, interleukin; mAb, monoclonal antibody; TSLP, thymic stromal lymphopoietin.

FcεR1 on the surface of the mast cells and basophils binds to the antigen, which induces cross linking of bound IgE.¹⁶ This leads to the release of inflammatory mediators including histamine, leukotriene, cytokines, and prostaglandin, leading to the development of an allergic reaction.¹⁵

ANTI-IMMUNOGLOBULIN E ANTIBODY

Omalizumab is a monoclonal antibody that targets the constant domain of the IgE molecule. Omalizumab binds free IgE, decreases its level in circulation, and prevents its binding to the surface of basophil and mast cell, hence suppressing them from degranulation on allergen exposure.¹⁷ Omalizumab is the most evaluated biologic in food allergy.

As a monotherapy, omalizumab was administered for 6 months in 14 patients with peanut allergy. A significant increase in the threshold of reactivity to peanut was observed during food challenges after 3 to 11 weeks of omalizumab, from a median of 80 mg to 6500 peanut protein. However, no additional changes in the peanut-eliciting dose were observed after 6 months of therapy.¹⁸ Another small trial demonstrated increase in tolerability to peanut after 24 weeks of omalizumab therapy compared with placebo.¹⁹ A more recent study demonstrated a significant increase in food allergen threshold (milk, egg, hazelnut, and wheat) after 4 months of omalizumab administered for treatment of asthma.²⁰ Interestingly, tolerated food was reintroduced in the patients' diet without the need of oral immunotherapy in these severely asthmatic patients.

On the other hand, omalizumab had been successfully used to facilitate desensitization of OIT in several clinical trials.^{21–26} We reported on the first trial using omalizumab as an adjunct therapy to peanut OIT in patients with very high peanut IgE (median

229 kU/L) who reacted to 50 mg peanut protein during entry food challenge. After receiving omalizumab only for 12 weeks, patients were rapidly desensitized to 2000 mg peanut protein over a median period of 8 weeks during which they received OIT combined with omalizumab.²³ A double-blind placebo-controlled milk OIT trial with omalizumab showed that although there was a significant reduction in adverse events in the omalizumab-treated arm, there was no difference in SU.²⁴ Omalizumab was also successfully used as an adjunct therapy in multi-food OIT, enabling safe and rapid desensitization.²⁶

One anticipated multisite double-blind placebo-controlled randomized trial will aim at evaluating omalizumab as a monotherapy and in combination with multi-food OIT (NCT03881696).

Ligelizumab (QGE031) is another promising monoclonal antibody that binds free serum IgE with much higher affinity than omalizumab.²⁷ To date, no clinical trial has evaluated ligelizumab for treatment of food allergy. However, Phase II trials in asthma (NCT01716754) and atopic dermatitis (NCT01552629) were completed, and Phase III chronic spontaneous urticarial (NCT02851277) is still ongoing.

ANTI-TH2 CYTOKINE ANTIBODIES

As noted previously, although omalizumab allowed for faster and safer food desensitization, it was not shown to improve the SU rate.^{22–24} Targeting other pathways that are involved in the allergic response has gained significant interest recently. Allergen-induced IL-4 expression in peripheral mononuclear cells was found to be associated with clinical allergy to milk and IgE-sensitization to milk and peanut.²⁸ Patients with mutations in IL-4 receptor alpha (IL-4R α) and IL13 were found to have an increased risk of food allergy.²⁹ Dupilumab is a human monoclonal IgG4 antibody that binds to the alpha subunit of IL-4R α and blocks IL-4 and IL-13 signaling. Dupilumab was approved by the FDA for treatment of adults with moderate to severe atopic dermatitis,³⁰ as an add-on maintenance therapy for moderate to severe asthma (with an eosinophilic phenotype or corticosteroid dependent) in patients age 12 years and older,³¹ and recently for treatment of chronic rhinosinusitis with nasal polyposis.³²

In patients who underwent peanut OIT initially facilitated by omalizumab,²³ we have shown that the suppressive function of peanut reactive Treg cells was recovered after blockade of IL-4 signaling.³³ Recently a 30-year-old patient with a history of allergic reaction to pistachio during food challenge and anaphylaxis to corn, received dupilumab for severe atopic dermatitis. Both pistachio and corn were subsequently tolerated during an open food challenge after 3 months of therapy.³⁴ There are currently 2 ongoing randomized placebo-controlled Phase II clinical trials evaluating dupilumab in food allergy. One of these studies is evaluating dupilumab as a monotherapy (NCT03793608) while the other as an adjunct therapy to peanut OIT (NCT03682770). Another single-site randomized Phase II trial is anticipated in patients with at least 3 food allergies, which aims at comparing safety and efficacy of dupilumab, omalizumab, or both as adjunct therapy to multi-food OIT (NCT03679676).

Blockage of IL-13 signaling alone has not been investigated yet in food allergy. Anti-IL-13 antibody (QAX576) was evaluated for treatment of eosinophilic esophagitis. Although it showed a decrease in esophageal eosinophilia, it did not lead to significant improvement in clinical symptoms.³⁵ Lebrikizumab is another IL-13 monoclonal antibody that has been investigated for treatment of asthma. In a Phase III trial in adults with mild to moderate asthma not receiving corticosteroids, therapy did not improve

lung function.³⁶ However, a recent meta-analysis of 5 randomized controlled trials concluded that lebrikizumab decreased the rate of asthma exacerbation and improved lung function in patients with uncontrolled asthma, especially those with elevated periostin level.³⁷

IL-5 is the main cytokine involved in activation of eosinophils. A Cochrane analysis supported the use of anti-IL-5 treatments as an adjunct to standard of care in people with severe eosinophilic asthma and poor control.³⁸ Mepolizumab and reslizumab, which are monoclonal antibodies against IL-5 and benralizumab, a monoclonal antibody against IL-5R α , are all FDA approved for treatment of eosinophilic asthma.³⁹ The value of targeting eosinophils in the treatment of IgE-mediated food allergy remains, however, unclear. To date, there are no reported trials evaluating these biologics in food allergy.

TH1 ADJUVANTS

TH1 adjuvants, such as TLRs, combined with an allergen may be used to skew the TH1:TH2 balance toward TH1 polarization.⁴⁰ Murine studies have shown that anaphylactic reactions were reduced when CpG oligodeoxynucleotide, a TLR agonist was combined with ovalbumin and peanut allergens.^{41–44} There are currently no trials evaluating CpG in food allergy. However, clinical improvement was reported in patients with allergic rhinitis given CpG coupled to ragweed allergen.^{45,46}

Monophosphoryl lipid A (MPL) is a TLR4 agonist that was also shown to be effective as an adjuvant therapy to immunotherapy for allergic rhinitis.^{47–49} Glucopyranosyl lipid A, a synthetic form of MPL, has shown promising results in a peanut-allergic mouse model.⁵⁰ It is currently being investigated in a Phase I trial as adjunctive therapy to peanut SLIT ([NCT03463135](#)).

Chitosan is a biodegradable polymer that was shown in a mouse model to be prevent peanut-induced anaphylaxis and suppress peanut-specific IgE and TH2 cytokines.⁵¹ It has not been evaluated yet for food allergy.

EPITHELIAL CELL-DERIVED CYTOKINES (INTERLEUKIN-33 AND THYMIC STROMAL LYMPHOPOIETIN) ANTIBODIES

As noted previously, antigen sensitization is associated with increased epithelial cell permeability.⁵² Epithelial cytokines thymic stromal lymphopoietin (TSLP) and IL-33 promote TH2 response.^{53,54} Targeting these cytokines could be a potential approach in treating food allergy.

Etokimab, also known as ANB020, is an anti-IL-33 antibody that has been evaluated in a Phase 2 trial in adults with peanut allergy. The results of this study have not been published yet ([NCT02920021](#)). Another trial is ongoing to evaluate its use in atopic dermatitis ([NCT03533751](#)).

Tezepelumab is a humanized monoclonal antibody against TSLP that was investigated in a Phase 2 clinical trial in adults with uncontrolled asthma. Patients who received tezepelumab had lower rates of asthma exacerbation compared with placebo.⁵⁵ In adults with moderate to severe atopic dermatitis treated with a combination of topical corticosteroids combined with tezepelumab or placebo, there was improvement in the eczema area and severity index in tezepelumab-treated patients, although it did not reach statistical significance.⁵⁶ Treatment-emergent adverse effects were similar in the 2 groups. Anti-TSLP therapy has not been evaluated yet in food allergy.

DNA VACCINES

DNA vaccines stimulate an immune response to a specific DNA-encoded protein inserted to a bacterial plasmid.⁵⁷ The immunogenicity of DNA vaccines was shown to be enhanced by inclusion of lysosomal-associated membrane protein-1 (LAMP-1).⁵⁸ After intradermal or intramuscular administration, uptake of the plasmid by antigen-presenting cells results in the synthesis of an allergen-LAMP fusion protein. The LAMP component directs the fusion protein toward cellular lysosomes where the allergen is subsequently processed and added to major histocompatibility complex-II antigens, which induces a CD4+ helper T-cell response.^{57,58} ASP0892 (ARA-LAMP-vax) is a recently developed single multivalent peanut (Ara h1, h2, h3) LAMP DNA Plasmid Vaccine. A Phase I trial is currently ongoing to evaluate its safety, tolerability, and subsequent immune responses in peanut-allergic adolescents when administered via the intradermal route ([NCT03755713](#)) after it was evaluated in adults ([NCT02851277](#)).

MODIFIED FOOD ALLERGEN PROTEINS

Using modified food allergen proteins is another approach that stipulates that desensitization may be achieved with lesser risk of allergic reactions compared with the natural protein. In a Phase I study by Wood and colleagues,⁵⁹ heat/phenol killed, *Escherichia coli* encapsulated, recombinant modified peanut proteins Ara h 1, Ara h 2, and Ara h 3 (EMP-123) was used for treatment of peanut allergy. A rectal administration of EMP-123 in 10 peanut-allergic patients resulted in frequent adverse events, including anaphylaxis in 20% of peanut-allergic patients, whereas no significant adverse events occurred in 5 healthy volunteers.

HAL-MPE1 is a chemically modified, aluminum hydroxide-adsorbed peanut extract for subcutaneous use, and is currently being evaluated in a Phase I trial that aims at assessing its safety in peanut-allergic adolescents and children ([NCT02991885](#)).

TARGETING THE MICROBIOME FOR THE TREATMENT OF FOOD ALLERGY

Manipulation of the microbiome may be considered for both preventive and therapeutic interventions.

Several studies evaluated the role of the gut microbiota in food allergy. There has been, however, significant heterogeneity between these studies in design, sample size, age at time fecal collection, methods of bacterial analysis, and geographic location among others.¹² Most studies evaluated subjects for evidence of sensitization to food (ie, positive food-specific skin or IgE) without history of food allergy per se. The small number of patients in these studies did not allow for robust statistical analysis of the effect of potential confounding variables, such as cesarean delivery, diet, antibiotic intake, number of siblings, infections, and pets.⁶⁰ We recently reported on a large longitudinal observational study in infants with a history of IgE-mediated allergic reaction to food confirmed by positive skin prick test and/or serum food-specific IgE. Fifty-six infants with food allergy and 98 healthy controls were enrolled. Stool samples were collected every 6 months for a total of 30 months; 16S ribosomal DNA sequencing showed no difference in ecological diversity or microbial richness. However, evolving dysbiosis was identified: compositional differences in relative abundance among 77 Operational Taxonomic Units were observed in the fecal microbiome between age-stratified food-allergic subjects and controls, some spanning several age groups, whereas others were significant only within a specific age group.¹⁴

The role of currently available probiotics in the prevention of treatment of food allergy is inconclusive. In a prospective randomized trial in infants with cow's milk allergy, those who received extensively hydrolyzed milk formula (EHMF) supplemented with *Lactobacillus* GG (LGG) acquired tolerance to cow's milk faster than those who were consuming EHMF without probiotic.⁶¹ On the other hand, in a double-blind placebo-controlled trial with 119 infants with cow's milk allergy fed either EHMF alone, or EHMF supplemented with *Lactobacillus casei* and *Bifidobacterium lactis*, there was no difference in the rate of acquisition of tolerance to cow's milk between the 2 groups.⁶² A systemic review and meta-analysis of 17 randomized controlled trials involving 2947 infants showed that when probiotics were given either only prenatally or postnatally, no effects of probiotics on atopy and food sensitivity (positive skin and/or specific IgE testing) were observed. When administered to pregnant mothers prenatally and to the child postnatally, the analysis suggested that probiotics could reduce the risk of atopy and food sensitivity.⁶³

A double-blind randomized placebo-controlled trial evaluated the effect of administering orally *Lactobacillus rhamnosus* CGMCC combined with peanut OIT for 18 months on SU. Eighty-two percent of subjects in the peanut OIT/probiotic were noted to have possible SU after withholding OIT for 2 to 5 weeks. The study, however, did not have a peanut OIT arm without probiotic or a probiotic arm without peanut OIT.⁶⁴ It is also possible that the higher rate of SU compared with other studies was affected in part by a shorter duration of interruption of therapy in some patients.

In *Il4ra*^{F709} mice that are genetically prone to food allergy, we found that bacteriotherapy with 6 commensal Clostridiales strains and separately with 5 Bacteroidales strains, chosen as representative of clusters impacted by the dysbiosis in infants, both prevented and treated food allergy. In addition, bacteriotherapy led to upregulation of RoR γ Treg cells, and decrease in total and ova-specific serum IgE, IL-4 production, and GATA3 expression by Treg cells.¹⁴ Protection from anaphylaxis was also noted when treating these mice with a single Clostridial species, *Subdoligranulum variabilis*, which was also impacted by the dysbiosis in food-allergic infants.¹⁴ In a different food allergy mouse model, *Anaerostipes caccae*, another Clostridial species, also protected against allergic reaction. Developing targeted bacterial therapies for food allergy may thus be promising for treatment and prevention of food allergy.

Another approach in microbial intervention is to attempt a more general modification of the gut microbiome. Fecal microbiota transplantation (FMT) is the transfer of stool from a healthy donor into the gastrointestinal tract of a diseased individual. FMT may be performed by different routes, including colonoscopy, nasogastric tube, or oral capsules. In humans, FMT has been successfully used to treat recurrent refractory *Clostridium difficile* colitis.⁶⁵ We and others have found that FMT using stools taken from healthy human infants and transplanted into a food-allergic mouse model protects from anaphylaxis after allergen exposure, whereas anaphylaxis was not abrogated when FMT was performed with stools taken from food-allergic infants.^{14,66} We are currently conducting a Phase I trial to evaluate the safety and efficacy of frozen encapsulated FMT peanut-allergic adults age 18 to 40 years (NCT02960074).

SUMMARY

There is currently no cure for food allergy. There is an unmet need to evaluate different therapeutic modalities that aims at abolishing or decreasing the risk of anaphylaxis and improving the quality of life of affected patients and their families. Trials are currently ongoing evaluating biologics, modified food proteins, DNA vaccines, and

FMT. Although these are exciting times for food allergy research, the safety, efficacy, long-term effect, and ultimately cost of these interventions will need to be carefully evaluated.

REFERENCES

1. Branum AM, Lukacs SL. Food allergy among U.S. children: trends in prevalence and hospitalizations. *NCHS Data Brief* 2008;(10):1–8.
2. Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics* 2011;128:e9–17.
3. Gupta RS, Warren CM, Smith BM, et al. Prevalence and severity of food allergies among US adults. *JAMA Netw open* 2019;2:e185630.
4. Sicherer SH, Sampson HA. Food allergy: epidemiology, pathogenesis, diagnosis, and treatment. *J Allergy Clin Immunol* 2014;133:291–307 [quiz: 308].
5. Patel N, Herbert L, Green TD. The emotional, social, and financial burden of food allergies on children and their families. *Allergy Asthma Proc* 2017;38:88–91.
6. Yee CS, Rachid R. The heterogeneity of oral immunotherapy clinical trials: implications and future directions. *Curr Allergy Asthma Rep* 2016;16:25.
7. Vickery BP, Vereda A, Casale TB, et al. AR101 oral immunotherapy for peanut allergy. *N Engl J Med* 2018;379:1991–2001.
8. Fleischer DM, Greenhawt M, Sussman G, et al. Effect of epicutaneous immunotherapy vs placebo on reaction to peanut protein ingestion among children with peanut allergy: the PEPITES randomized clinical trial. *JAMA* 2019;321(10):946–55.
9. Vickery BP, Scurlock AM, Kulis M, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. *J Allergy Clin Immunol* 2014;133:468–75.
10. Syed A, Garcia MA, Lyu SC, et al. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). *J Allergy Clin Immunol* 2014;133:500–10.
11. Chu DK, Wood RA, French S, et al. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. *Lancet* 2019;393(10187):2222–32.
12. Rachid R, Chatila TA. The role of the gut microbiota in food allergy. *Curr Opin Pediatr* 2016;28:748–53.
13. Stefka AT, Feehley T, Tripathi P, et al. Commensal bacteria protect against food allergen sensitization. *Proc Natl Acad Sci U S A* 2014;111:13145–50.
14. Abdel-Gadir A, Stephen-Victor E, Gerber GK, et al. Microbiota therapy acts via a regulatory T cell MyD88/ROrgammat pathway to suppress food allergy. *Nat Med* 2019;25(7):1164–74.
15. Bauer RN, Manohar M, Singh AM, et al. The future of biologics: applications for food allergy. *J Allergy Clin Immunol* 2015;135:312–23.
16. Sampath V, Sindher SB, Zhang W, et al. New treatment directions in food allergy. *Ann Allergy Asthma Immunol* 2018;120:254–62.
17. Liu J, Lester P, Builder S, et al. Characterization of complex formation by humanized anti-IgE monoclonal antibody and monoclonal human IgE. *Biochemistry* 1995;34:10474–82.
18. Savage JH, Courneya JP, Sterba PM, et al. Kinetics of mast cell, basophil, and oral food challenge responses in omalizumab-treated adults with peanut allergy. *J Allergy Clin Immunol* 2012;130:1123–9.e2.

19. Sampson HA, Leung DY, Burks AW, et al. A phase II, randomized, double-blind, parallel group, placebo-controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy. *J Allergy Clin Immunol* 2011;127:1309–10.e1.
20. Fiocchi A, Artesani MC, Riccardi C, et al. Impact of omalizumab on food allergy in patients treated for asthma: a real-life study. *J Allergy Clin Immunol Pract* 2019;7(6):1901–9.e5.
21. Nadeau KC, Schneider LC, Hoyte L, et al. Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. *J Allergy Clin Immunol* 2011;127:1622–4.
22. MacGinnitie AJ, Rachid R, Gragg H, et al. Omalizumab facilitates rapid oral desensitization for peanut allergy. *J Allergy Clin Immunol* 2017;139:873–81.e8.
23. Schneider LC, Rachid R, LeBovidge J, et al. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. *J Allergy Clin Immunol* 2013;132:1368–74.
24. 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;137:1103–10.e11.
25. Andorf S, Manohar M, Dominguez T, et al. Observational long-term follow-up study of rapid food oral immunotherapy with omalizumab. *Allergy Asthma Clin Immunol* 2017;13:51.
26. Andorf S, Purington N, Block WM, et al. Anti-IgE treatment with oral immunotherapy in multifood allergic participants: a double-blind, randomised, controlled trial. *Lancet* 2018;3:85–94.
27. Kocaturk E, Zuberbier T. New biologics in the treatment of urticaria. *Curr Opin Allergy Clin Immunol* 2018;18:425–31.
28. Sicherer SH, Wood RA, Stablein D, et al. Immunologic features of infants with milk or egg allergy enrolled in an observational study (Consortium of Food Allergy Research) of food allergy. *J Allergy Clin Immunol* 2010;125:1077–83.e8.
29. Zitnik SE, Ruschendorf F, Muller S, et al. IL13 variants are associated with total serum IgE and early sensitization to food allergens in children with atopic dermatitis. *Pediatr Allergy Immunol* 2009;20:551–5.
30. Beck LA, Thaci D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med* 2014;371:130–9.
31. Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med* 2018;378:2475–85.
32. Han JK, Bachert C, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with chronic rhinosinusitis with nasal polyps: results from the randomized phase 3 sinus-24 study. *J Allergy Clin Immunol* 2019;143:AB422.
33. Abdel-Gadir A, Schneider L, Casini A, et al. Oral immunotherapy with omalizumab reverses the Th2 cell-like programme of regulatory T cells and restores their function. *Clin Exp Allergy* 2018;48:825–36.
34. Rial MJ, Barroso B, Sastre J. Dupilumab for treatment of food allergy. *J Allergy Clin Immunol Pract* 2019;7(2):673–4.
35. Rothenberg ME, Wen T, Greenberg A, et al. Intravenous anti-IL-13 mAb QAX576 for the treatment of eosinophilic esophagitis. *J Allergy Clin Immunol* 2015;135:500–7.
36. Hanania NA, Korenblat P, Chapman KR, et al. Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials. *Lancet Respir Med* 2016;4:781–96.

37. Liu Y, Zhang S, Chen R, et al. Meta-analysis of randomized controlled trials for the efficacy and safety of anti-interleukin-13 therapy with lebrikizumab in patients with uncontrolled asthma. *Allergy Asthma Proc* 2018;39:332–7.
38. Farne HA, Wilson A, Powell C, et al. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev* 2017;(9):CD010834.
39. Matera MG, Calzetta L, Rogliani P, et al. Monoclonal antibodies for severe asthma: pharmacokinetic profiles. *Respir Med* 2019;153:3–13.
40. Keet CA, Wood RA. Emerging therapies for food allergy. *J Clin Invest* 2014;124:1880–6.
41. Adel-Patient K, Ah-Leung S, Bernard H, et al. Oral sensitization to peanut is highly enhanced by application of peanut extracts to intact skin, but is prevented when CpG and cholera toxin are added. *Int Arch Allergy Immunol* 2007;143:10–20.
42. Kulis M, Gorentla B, Burks AW, et al. Type B CpG oligodeoxynucleotides induce Th1 responses to peanut antigens: modulation of sensitization and utility in a truncated immunotherapy regimen in mice. *Mol Nutr Food Res* 2013;57:906–15.
43. San Roman B, Irache JM, Gomez S, et al. Co-delivery of ovalbumin and CpG motifs into microparticles protected sensitized mice from anaphylaxis. *Int Arch Allergy Immunol* 2009;149:111–8.
44. Xu W, Tamura T, Takatsu K. CpG ODN mediated prevention from ovalbumin-induced anaphylaxis in mouse through B cell pathway. *Int Immunopharmacol* 2008;8:351–61.
45. Creticos PS, Schroeder JT, Hamilton RG, et al. Immunotherapy with a ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis. *N Engl J Med* 2006;355:1445–55.
46. Tulic MK, Fiset PO, Christodoulouopoulos P, et al. Amb a 1-immunostimulatory oligodeoxynucleotide conjugate immunotherapy decreases the nasal inflammatory response. *J Allergy Clin Immunol* 2004;113:235–41.
47. Patel P, Holdich T, Fischer von Weikersthal-Drachenberg KJ, et al. Efficacy of a short course of specific immunotherapy in patients with allergic rhinoconjunctivitis to ragweed pollen. *J Allergy Clin Immunol* 2014;133:121–9.e1-2.
48. Pfaar O, Barth C, Jaschke C, et al. Sublingual allergen-specific immunotherapy adjuvanted with monophosphoryl lipid A: a phase I/IIa study. *Int Arch Allergy Immunol* 2011;154:336–44.
49. Rosewich M, Schulze J, Fischer von Weikersthal-Drachenberg KJ, et al. Ultra-short course immunotherapy in children and adolescents during a 3-yr post-marketing surveillance study. *Pediatr Allergy Immunol* 2010;21:e185–9.
50. Soos TJ, Li L, Graver K, et al. Glucopyranosyl Lipid a (GLA) a Toll-like receptor 4 (TLR4) agonist for use as an adjuvant in combination with peanut allergen immunotherapy. *J Allergy Clin Immunol* 2016;137:AB129.
51. Bae MJ, Shin HS, Kim EK, et al. Oral administration of chitin and chitosan prevents peanut-induced anaphylaxis in a murine food allergy model. *Int J Biol Macromol* 2013;61:164–8.
52. Turner JR. Intestinal mucosal barrier function in health and disease. *Nat Rev Immunol* 2009;9:799–809.
53. Chu DK, Llop-Guevara A, Walker TD, et al. IL-33, but not thymic stromal lymphopoietin or IL-25, is central to mite and peanut allergic sensitization. *J Allergy Clin Immunol* 2013;131:187–200.e1-8.
54. Jang S, Morris S, Lukacs NW. TSLP promotes induction of Th2 differentiation but is not necessary during established allergen-induced pulmonary disease. *PLoS One* 2013;8:e56433.

55. Corren J, Parnes JR, Wang L, et al. Tezepelumab in adults with uncontrolled asthma. *N Engl J Med* 2017;377:936–46.
56. Simpson EL, Parnes JR, She D, et al. Tezepelumab, an anti-thymic stromal lymphopoietin monoclonal antibody, in the treatment of moderate to severe atopic dermatitis: A randomized phase 2a clinical trial. *J Am Acad Dermatol* 2019;80:1013–21.
57. Liu MA. DNA vaccines: an historical perspective and view to the future. *Immunol Rev* 2011;239:62–84.
58. Su Y, Connolly M, Marketon A, et al. CryJ-LAMP DNA vaccines for Japanese red cedar allergy induce robust Th1-type immune responses in murine model. *J Immunol Res* 2016;2016:4857869.
59. 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;68:803–8.
60. Molloy J, Allen K, Collier F, et al. The potential link between gut microbiota and IgE-mediated food allergy in early life. *Int J Environ Res Public Health* 2013;10:7235–56.
61. Berni Canani R, Nocerino R, Terrin G, et al. Effect of Lactobacillus GG on tolerance acquisition in infants with cow's milk allergy: a randomized trial. *J Allergy Clin Immunol* 2012;129:580–2, 582.e1-5.
62. Hol J, van Leer EH, Elink Schuurman BE, et al. The acquisition of tolerance toward cow's milk through probiotic supplementation: a randomized, controlled trial. *J Allergy Clin Immunol* 2008;121:1448–54.
63. Zhang GQ, Hu HJ, Liu CY, et al. Probiotics for prevention of atopy and food hypersensitivity in early childhood: a PRISMA-compliant systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2016;95:e2562.
64. Tang ML, Ponsonby AL, Orsini F, et al. Administration of a probiotic with peanut oral immunotherapy: a randomized trial. *J Allergy Clin Immunol* 2015;135:737–44.e8.
65. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med* 2013;368:407–15.
66. Feehley T, Plunkett CH, Bao R, et al. Healthy infants harbor intestinal bacteria that protect against food allergy. *Nat Med* 2019;25:448–53.
67. Leung DY, Sampson HA, Yunginger JW, et al. Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med* 2003;348:986–93.
68. Dispenza MC, Pongracic JA, Singh AM, et al. Short-term ibrutinib therapy suppresses skin test responses and eliminates IgE-mediated basophil activation in adults with peanut or tree nut allergy. *J Allergy Clin Immunol* 2018;141:1914–6.e7.
69. Berni Canani R, Di Costanzo M, Bedogni G, et al. Extensively hydrolyzed casein formula containing Lactobacillus rhamnosus GG reduces the occurrence of other allergic manifestations in children with cow's milk allergy: 3-year randomized controlled trial. *J Allergy Clin Immunol* 2017;139:1906–13.e4.