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REVIEW ARTICLE

Food allergy, mechanisms, diagnosis and treatment: Innovation through a multi-targeted approach

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Abstract

The incidence of food allergy (FA) has continued to rise over the last several decades, posing significant burdens on health and quality of life. Significant strides into the advancement of FA diagnosis, prevention, and treatment have been made in recent years. In an effort to lower reliance on resource-intensive food challenges, the field has continued work toward the development of highly sensitive and specific assays capable of high-throughput analysis to assist in the diagnosis FA. In looking toward early infancy as a critical period in the development of allergy or acquisition of tolerance, evidence has increasingly suggested that early intervention via the early introduction of food allergens and maintenance of skin barrier function may decrease the risk of FA. As such, large-scale investigations are underway evaluating infant feeding and the impact of emollient and steroid use in infants with dry skin for the prevention of allergy. On the other end of the spectrum, the past few years have been witness to an explosive increase in clinical trials of novel and innovative therapeutic strategies aimed at the treatment of FA in those whom the disease has already manifested. A milestone in the field, 2020 marked the approval of the first drug, oral peanut allergen, for the indication of peanut allergy. With a foundation of promising data supporting the safety and efficacy of single- and multi-allergen oral immunotherapy, current efforts have turned toward the use of probiotics, biologic agents, and modified allergens to optimize and improve upon existing paradigms. Through these advancements, the field hopes to gain footing in the ongoing battle against FA.

KEYWORDS
diagnostics, food allergy, oral immunotherapy, prevention, treatment

1 | INTRODUCTION

Food allergy (FA) is a significant health burden globally (Figure 1). Studies estimating FA prevalence have varied, depending on diagnostic method, number and type of allergens, and geographical location; however, there is general consensus that FA is increasing. The population-based Melbourne HealthNuts and SchoolNuts studies estimated FA using oral food challenges (OFC), the gold standard for diagnosing FA. The study found a FA prevalence rate of 10% in infants and 4% to 5% in older children and young adolescents.[1] In the US, using cross-sectional population-based surveys, FA prevalence has been estimated at approximately 8% in children and 11% in adults[2,3]; In Europe, using data from the EuroPrevall-iFAAM birth cohort, prevalence in children was found to be much lower at 1.4–3.8%.[4,5]

Sayantani B. Sindher and Andrew Long contributed equally to the manuscript.

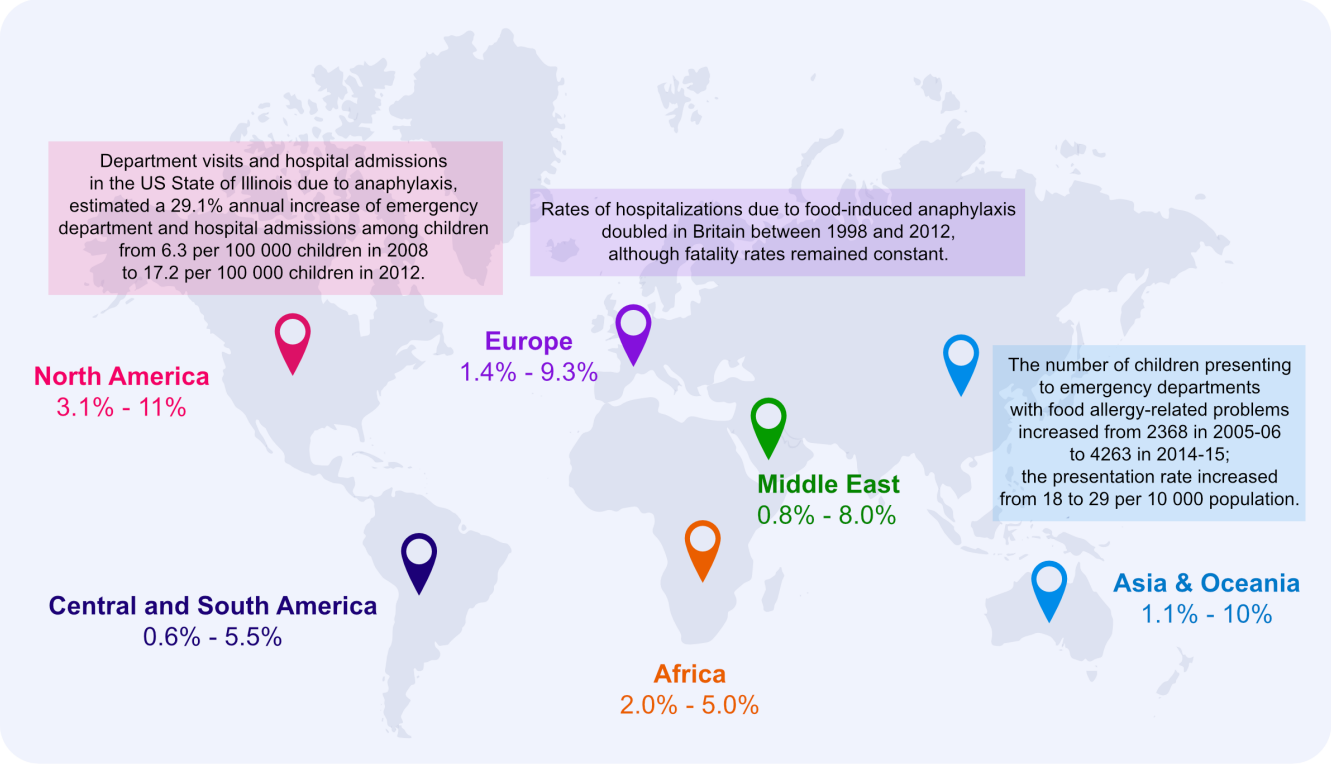

FIGURE 1 Prevalence of food allergy varies globally. Food allergy-associated hospitalization admission rates suggest that rates of FA has increased over the last few decades[1-4,11,12]

FA additionally presents with significant impacts to quality of life[6,7] and a high economic burden.[8] While the first approved treatment for peanut allergy (PA) is now available,[9] the current standard of care for other food allergens remains strict avoidance. Advancements in the field of allergen immunotherapy and the development of biologics and other novel therapies have continued to push towards safe and effective options for FA treatment.[10] Additionally, recent efforts have shifted focus to investigate innovations in the realm of diagnostics, endotyping, and primary prevention. In this review, we provide an overview of major recent developments in the diagnosis, prevention, and treatment of FA (Box 1).

2 | DIAGNOSIS AND ENDOTYPING

The gold standard for the diagnosis of FA remains the double-blind placebo-controlled food challenge (DBPCFC); however, they are time-intensive with high-risk of severe reaction, necessitating a need for alternative diagnostic techniques (Figure 2). Allergen-specific IgE (sIgE) assays are readily available in clinical settings but have a high rate of false positives as they cannot distinguish true FA from sensitivity without clinical allergy. The ImmunoCAP assay is a fluorescent method, which is currently the standard for sIgE quantification. It is sensitive but requires a large amount of blood, which can be problematic when testing young children. A method that has shown to be comparable to ImmoCAP is IMMULITE, a chemiluminescent method.[13] Recently, LuLISA, an bioluminescent method, which requires 1 μl or less of plasma sample has been published.[14] Additionally, a peanut bead-based epitope assay was developed using the LEAP cohort and validated in CoFAR-2 and POISED studies. It uses two sIgE antibodies in sequential fashion to diagnose PA and has demonstrated good sensitivity (92.3%), specificity (94.1%), and accuracy (93.4% concordance with DBPCFC). Although requiring less than 100 μl of plasma/serum and being easily adapted for high-throughput use in clinical labs, gaps in the molecular characterization of non-peanut allergens has limited its use.[15]

Beyond IgE characterization, the potential of basophil activation tests (BAT) has been increasingly recognized in recent years.[16,17] However, the effectiveness of BAT differs significantly between allergens.[17-19] Despite variation in sensitivity, BAT has demonstrated high levels of specificity enabling it to complement skin-prick and sIgE tests, which lack specificity but provide considerable sensitivity. Using BAT as a second-round diagnostic test after skin-prick and sIgE pre-screening was shown to reduce the number of required diagnostic OFC by 5–15% for peanut, sesame, and cashew.[20] The MONAS study found that a single BAT was efficacious in predicting clinical allergy status across peanut (AUROC 0.98), cashew (0.97), hazelnut (0.92), pistachio (0.95), and walnut (0.97), outperforming sIgE testing for peanut and hazelnut in a sub-analysis of sensitized patients undergoing OFC.[17] In addition to a potential role in the diagnosis of FA, BAT may also predict response to OIT.[19] The POISED study found that patients who failed DBPCFCs after a period of desensitization followed by peanut avoidance had higher %CD63^{high} basophils upon peanut stimulation and had significantly higher Ara h 1, Ara h

BOX 1 Key findings

Diagnosis

- Bead-Based Epitope Assay can be performed on small quantities of blood, can be easily adapted to clinical diagnostic labs for the diagnosis of peanut allergy, and has a 93.4% concordance with food challenge outcomes.
- In the POISED study sustained unresponsiveness to peanut was observed in patients with low basophil activation at baseline and those with a greater than 80% reduction in peanut-induced basophil activation after OIT.

Prevention

- Early introduction of peanut reduces the risk of developing peanut allergies by 80%, which was first observed in the LEAP trial. Other recent studies have shown that early introduction of egg and dairy reduces the cumulative incidence of egg allergy by 3 years from 2.2% to 0.2% and incidence of milk allergy at 6 months from 6.8% to 0.8%.
- In the LEAP and EAT studies, both the severity and duration of AD in the 1st year of life were predictors of peanut allergy and sensitization at 1 year of age.

Treatment

- Numerous landmark studies have paved the way for the first FDA and EMA approved peanut (*Arachis hypogaea*) Allergen Powder-dnfp in 2020 for children 4–17 years old.
- The IMPACT trial published in 2022, demonstrated that peanut OIT is safe in children 1–3 years of age inducing desensitization up to 5000 mg of peanut protein in 71% of patients.
- The use of adjunct biologic therapies with single and multifood OIT has exploded in clinical research trials. The most study biologic, Omalizumab, have demonstrated safety, efficacy, and feasibility of achieving desensitization to volumes of allergen beyond accidental ingestion. Compared to placebo, those receiving omalizumab had a 41% lower median per-participant percentage of doses associated with AEs.

2, Ara h 3, and sIgE/total IgE than those who passed DBPCFCs.[21] Classification of patients into "non/low", "intermediate", or "high" basophil responders at baseline was additionally able to predict success of DBPCFCs following treatment. Sustained unresponsiveness (SU) to peanut was observed in patients with low basophil activation at baseline and those with a greater than 80% reduction in peanut-induced basophil activation after OIT,[22] supporting the utility of BAT in predicting and monitoring response to OIT. These new technologies including others using novel gating strategies with optimization of storage and automation of measurements and analysis may enable routine high-throughput analysis in the future.[19,23-25]

Mast cell activation tests (MAT) is another in vitro diagnostic test, similar to BAT. The BAT uses whole blood whereas the MAT uses plasma or serum to sensitize mast cells. Expression of activation markers are measured on stimulation with allergen. The MAT has similar specificity in the diagnosis of PA but lower sensitivity.[26] Ongoing research and novel biomarkers in addition to IgE and basophil/mast activation biomarkers for diagnosis of FA are being developed.[27-29]

In addition to the inherent risks associated with DBPCFCs, there exists considerable variation across trial design, providers, and academic sites making DBPCFCs challenging to standardize. Several groups, including DeFASe,[30] Dribin et al.,[31] CoFAR,[32] and others[33] are attempting to more uniformly approach the characterization of reactions during food challenges through standardized grading scales for FA-related adverse events (AEs). As there is wide variability of AE severity, there is also the push to understand and develop tools for prediction of patient-specific response to DBPCFC.[34-37] These tools can assist in diagnostic and treatment strategies in those at risk for the most severe reactions.

Large-scale omics approaches have been an invaluable asset for the identification of diagnostic and prognostic markers, as well as for defining disease endotypes for a wide variety of diseases and pathologies,[38-40] however, so far, there has been limited application of these approaches to FA. Recent and previous studies have used approaches such as transcriptomics, epigenomics to identify markers for processes such as reaction diagnosis of allergy, reaction severity and outcomes during OIT, which may lead to innovative improvements to standard clinical assays.[28,41-48] However, omics approaches would be particularly valuable for identifying patients who are at risk of development food allergy in the future, which we currently have no means of predicting. A large-scale unbiased multi-omics approach, ideally from a birth cohort, could be used to identify biomarkers for patients who develop FA later in life as well as disease trajectories and endotypes of FA, which would allow us to effectively manage food allergy and potentially employ novel individualized preventative strategies.

2.1 | Prevention

A number of studies have demonstrated that early introduction of peanuts reduces the risk of developing peanut allergies by up to 80% with sustained effects through early childhood.[49-51] This risk reduction has also been observed by many studies for early introduction of egg allergy. When hen's egg is introduced to infants by 1 year of age, cumulative incidence of egg allergy was reduced at 3 years from 2.2% to 0.2%.[52] For other food allergens, the evidence is weaker and further studies are needed to determine whether early introduction decreases risk of allergy. The EAT Study found no effect of early introduction of milk, wheat, fish and sesame at 4–6 months on risk of food allergies in the intention to treat analysis.[53] However, a more recent randomized controlled study found that the introduction of

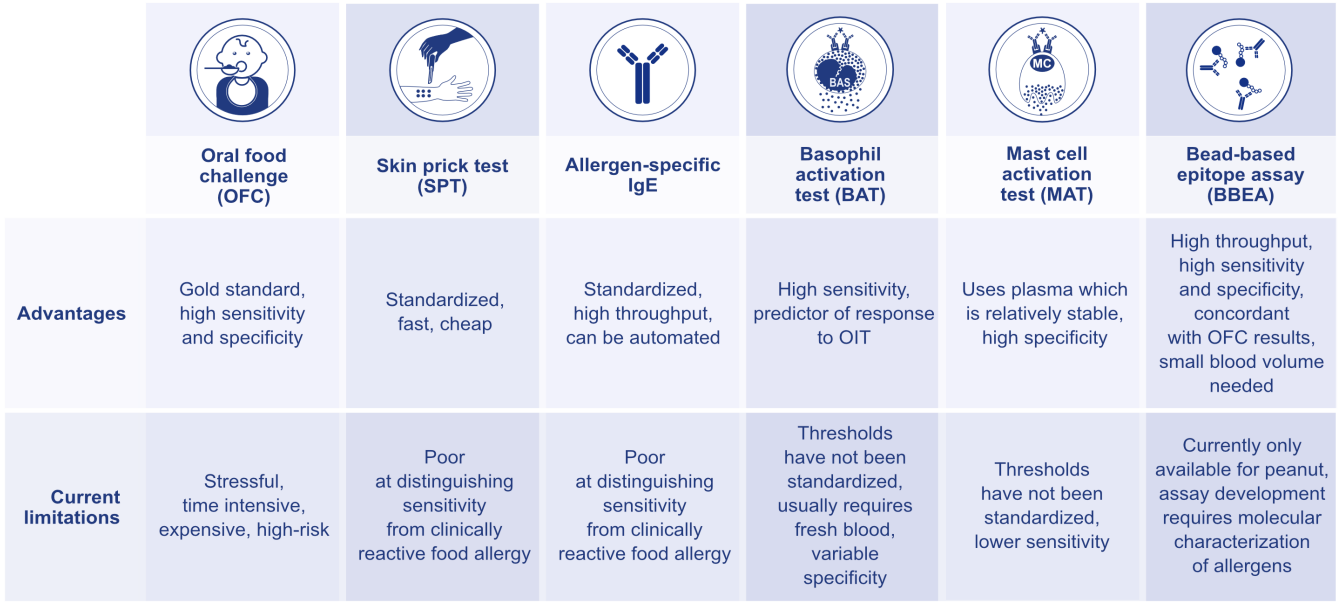

FIGURE 2 Routine diagnostic tests for food allergy include oral food challenges, skin-prick tests, and allergen-specific IgE. Other promising tests in development and currently limited to research settings include basophil activation test, mast cell activation test, and bead-based epitope assay

cow's milk formula at 1–2 months reduced the cumulative incidence of milk allergy at 6 months from 6.8% to 0.8%.[54]

Additionally, a pilot study demonstrated that compared to placebo (flax seeds) daily supplementation of a blend of 16 unique allergenic foods in infants 5–11 months of age over a 28-day period was well-tolerated with no significant differences in AEs.[55] These findings suggest that the early introduction of single allergens, or simultaneous introduction of multiple allergens, may be protective against FA. However, besides allergen types, questions such as age of allergen introduction, allergen amounts, and infant demographics (high risk or general population) needs further evaluation.[56] Other birth cohort studies, such as PARIS and ELFE are evaluating whether breastfeeding, consumption of different infant formulas such as regular, pre−/probiotics, partially hydrolyzed with hypoallergenic label, extensively hydrolyzed, soya, long chain poly unsaturated fatty acids (docosahexaenoic acid, arachidonic acid, and eicosatetraenoic acid) play a role in the prevention of FAs.[57,58]

While early ingestion of food generally promotes the induction of natural tolerance, exposure of food allergens through an impaired skin barrier may promote the development of FA.[59] Unsurprisingly, dry skin, as measured by transepidermal water loss (TEWL), and atopic dermatitis (AD) have been identified as risk factors for the development of FA.[60] Recent evaluation of moisturizers to prevent dry skin and reduce TEWL have presented conflicting results[51,61,62]; however, this may be due to the types of moisturizers used. The use of moisturizers containing food components such as olive oil and oat were associated with an increased risk of FA development, with each additional weekly application of moisturizers corresponding to an adjusted odds and risk ratio of 1.20 and 1.47, respectively.[63-65] In contrast, studies employing moisturizers, such as trilipid creams, that do not contain food allergen components and more closely mimic the skin microenvironment have indeed observed reductions in food sensitization[66] accompanied by increases in peanut-specific IgG, decreases in peanut-specific IgE, and a shift towards tolerogenic T cells.[61,62] A multi-center, phase II trial, the SEAL Study (Stopping Eczema and Allergy, NCT03742414), is investigating the efficacy of proactive daily trilipid skin barrier cream or commercial moisturizer with concomitant topical steroid use as needed compared to reactive care only in infants who have already developed AD or eczema by 12 weeks of age. The trial seeks to determine whether such interventions are able to reduce the occurrence and severity of atopy in early life, and, ultimately, prevent the subsequent development of FA. Further investigation is needed to determine optimal strategies across a multitude of topical agents that vary significantly in composition. Pre- and postnatal vitamin D supplements have also been proposed for the prevention of FA; however, at this time, the data from these studies are mixed and a clear conclusion has yet to be reached.[67-75]

2.2 | Therapy

Recent years have witnessed significant developments in the pursuit of safe and effective treatment options for those with FA[76-78] (Table 1). Landmark studies demonstrating the safety, efficacy of desensitization, and improvements in patient quality of life with oral immunotherapy (OIT) for food allergens led to the approval of peanut (*Arachis hypogaea*) Allergen Powder-dnfp, the first oral peanut agent approved by the FDA and EMA for use in FA.[9,78-81] Durability of desensitization following therapy, however, is still under question. The IMPACT study demonstrated that peanut OIT is safe in children 1–3 years of age, inducing desensitization up to 5000 mg of peanut

TABLE 1 Summary of ongoing food allergy clinical trials

Intervention			Trial number(s)	Phase	Population	Primary endpoint
Single-allergen Immunotherapy	Oral Immunotherapy	Peanut, ADP101[a], CNP-201[b], INP20[c], cow's Milk, baked cow's milk, hen's egg, shrimp, cashew	NCT04856865, NCT04974970, NCT03504774, NCT04222491, NCT03462030, NCT03736447, NCT05250856, NCT04950504, NCT04163562, NCT03251508	I-III	Ranging from 1-65 yo with at least 1 food allergy	Cumulative tolerated dose after food challenge; proportion of patients passing food challenge; number of adverse events; number of patients with dose-limiting toxicity; serum cytokines, ratio of sIgE/sIgG, alterations in immune cells
	Epicutaneous Immunotherapy	Peanut	NCT03211247	III	1-3 yo with peanut allergy	Differences between the percentage of treatment responders in the active Viaskin Peanut group compared to the placebo group. [Time Frame: Month 12]
		Milk	NCT02223182	II	2-17 yo with milk allergy	Differences between the percentage of treatment responders in the active Viaskin Milk group compared to the placebo group. [Time Frame: Month 12]
	Oral Mucosal Immunotherapy	INT301: Peanut allergen-containing toothpaste	NCT04603300	I	Adults with peanut allergy	To evaluate the safety of INT301 compared to placebo as measured by dose escalation during study.
Multi-allergen Immunotherapy	Oral Immunotherapy	Peanut and tree nuts Tree nuts	NCT03799328, NCT04801823	II-III	6 mo-5 yo with multi-food allergy (2-5 foods), 4-11 mo with peanut allergy	Cumulative tolerated dose after food challenge; changes in sIgG4; difference in the proportion of participants with clinical confirmed tree nut allergy at 18 months of age [Time Frame: 18 months of age]
Biologic Agents +/- OIT	Anti-IgE	Omalizumab +/- multi-allergen OIT	NCT03881696	III	1-56 yo with multi-food Peanut + 2 additional allergens (milk, egg, wheat, cashew, hazelnut, walnut)	Number of participants to successfully consume a single dose of ≥ 600 mg of peanut protein
		Omalizumab + multi-allergen OIT	NCT04045301	IIb	6-25 yo with multi-food allergy (≥3 foods)	Efficacy of omalizumab at decreasing time-to-maintenance (1500mg total protein) [Time Frame: 52 weeks]
		Ligelizumab	NCT04984876	III	6-55 yo with peanut allergy	Proportion of participants to tolerate a single dose of ≥ 600 mg of peanut protein at week 12. [Time Frame: 12 weeks]
	Anti-IL4rα	Dupilumab	NCT03793608	II	6-17 yo with peanut allergy	Proportion of patients treated with dupilumab monotherapy that pass DBPCFC with peanut protein [Time Frame: week 24)
		Dupilumab + AR101 (peanut oral immunotherapy)	NCT03682770	II	6-17 yo patients with peanut allergy	Proportion of patients who successfully complete an exit food challenge with 2044 mg cumulative peanut protein [Time Frame: Up to 40 weeks]

[a]Multifood oral immunotherapy product.

[b]Nanoparticle-encapsulated peanut protein.

[c]Peanut oral immunotherapy product.

protein in 71% of patients.[82] Remission rates were highly enriched in younger patients, suggesting that desensitization within a critical window may lead to more permanent immune changes. Similarly, the POISED study, a long-term trial of peanut OIT in patients aged 7–55 years highlights that SU is only achievable in less than 35% of those who are successfully desensitized, and SU through the course of a year is even less (13%).[21]

Despite the efficacy of OIT in desensitization, the daily consumption of allergenic foods can be burdensome, stressful, and marked with dose-related AEs, making continued compliance challenging. Designed to counter some of these difficulties, epicutaneous immunotherapy (EPIT) employs a skin patch system for continuous, non-invasive delivery of the food allergen. Initial results have demonstrated modest success, with peanut EPIT providing improvements in quality of life and improving threshold sensitivity to one peanut (300 mg protein) in 35.3% after 12 months of therapy (PEPITES)[83] and to 444 mg peanut protein in 21.7% of patients after 130 weeks of desensitization.[84] Rates of adherence with EPIT are high (96%) and although reactions are common (77.6%), they are mild and local.[84-86] Although EPIT achieves lower sensitivity thresholds than OIT initially, threshold sensitivity appears to improve over time. In addition to EPIT, sublingual immunotherapy (SLIT) is another alternative to OIT, which has proven to be safe and effective.[87,88] Peanut SLIT induced desensitization in 25% and SU in 20.8% of patients after 3–5 years of treatment.[89] Other alternatives to oral exposure are currently under investigation, including a Phase I clinical trial assessing the safety and feasibility of INT301, a toothpaste containing peanut protein, targeting peanut concentrations between SLIT and OIT. Despite oral delivery, INT301 is hoped to elicit fewer systemic side effects compared to OIT as the majority of the agent is expelled after brushing, minimizing gastrointestinal (GI) contact with the allergen.

Growing data support the link between the microbiota and immune system and modulation of gut microbiota through the introduction of new bacterial species or manipulation of existing microbes via specific probiotic supplementation has been proposed as treatment for FA.[90-92] In a phase II study of peanut OIT with adjunct *Lactobacillus rhamnosus* GG ATCC 53103, adjuvant probiotic therapy slightly, but significantly, reduced the exposure-adjusted incidence of AEs by about 8% in comparison to OIT with placebo probiotic; with a more notable (24%) reduction in exposure-adjusted incidence of AEs in children 1–5 years of age.[93] Further research into the use of an alternative probiotic, *Bifidobacterium bifidum* TMC3115, in infants aged 0.5 to 12 months of age with cow's milk allergy found reduced allergic symptom scores in the GI tract ($p = 0.001$), respiratory tract ($p = 0.002$), and skin ($p = 0.011$) compared to placebo after 6 months of supplementation, with decreased serum levels of TNFα, IL-1β, and IL-6 ($p \leq 0.001$).[94]

In addition to studies investigation single bacterial strains as adjunctive treatment for FA, other clinical trials investigating the broader modulation of the microbiome in those with FA are underway. A phase I/II study, is currently evaluating the use of an orally administered combination of dormant commensal bacteria (VE416) prior to or in combination with peanut OIT, with or without pretreatment with vancomycin, in those with PA (NCT03936998). Another study is evaluating the efficacy of encapsulated fecal microbiota transplantation delivered orally with or without pretreatment with antibiotics in those with PA (NCT02960074). By attempting to augment or replace the microbiome with that of those without FA, the approach may display an advantage over strategies limited to a single strain. The relationship between the microbiome and the immune system is still not well understood. The microbiome may create a tolerogenic environment through maintenance of the intestinal epithelial barrier, modulation of tolerogenic immune populations such as RORγt+− and Foxp3+−expressing Tregs, and alterations in metabolism,[95,96] however, further research is needed before we can effectively target the underlying microbial dysbiosis for treatment of FA.

Initial OIT studies were restricted to treatment of patients with a single FA and did not address the approximately 30% and 45% of children and adults, respectively, who are allergic to more than one food.[3] In recent years, however, a growing number of trials have demonstrated that simultaneous desensitization to multiple food allergens can be facilitated through the concomitant use of biologic agents. By selectively inhibiting specific mediators of the allergic pathway, these adjunct therapies are proposed to transiently reduce the likelihood of allergic reaction (Figure 3). The most studied biologic, omalizumab, an anti-IgE antibody, has proven to be safe and effective as an adjunct to multi-allergen OIT,[77,97] achieving desensitization to amounts of allergen beyond accidental ingestion (1–2 g protein per food).[98-100] Compared to placebo, participants receiving adjunct omalizumab prior to and during multifood OIT experienced reductions in the severity of AEs and a lower median per-participant percentage of their OIT doses associated with any AE (68% vs 27%; p = 0·0082), with GI events reported as the most common AE in both groups.[98,101] Ligelizumab, another anti-IgE agent with higher binding affinities for free IgE compared to omalizumab, is currently under investigation for peanut allergic patients (NCT04984876).[102]

Despite the promising data thus far, questions remain regarding the optimal use of biologics, such as dosing, inter-patient variability in response to therapy, and duration of pre- and concomitant treatment.[97] Studies investigating these questions are currently underway, including the BOOM and OUtMATCH studies. The BOOM study seeks to evaluate the use of an alternative weight-based dosing strategy for omalizumab in combination with multi-allergen OIT (NCT04045301). In parallel, OUtMATCH, a large-scale, multi-stage phase III study sponsored by the National Institutes of Health is investigating the use of variable-duration omalizumab therapy for multifood allergy, with or without multi-allergen OIT, in addition to long-term follow-up monitoring the post-treatment transition to daily consumption of real-food equivalents (NCT03881696).

While omalizumab has shown significant promise in promoting safe and rapid desensitization to multiple foods through IgE suppression, other clinical trials are focusing on broader targets in the allergic pathway in efforts to further minimize AEs and promote

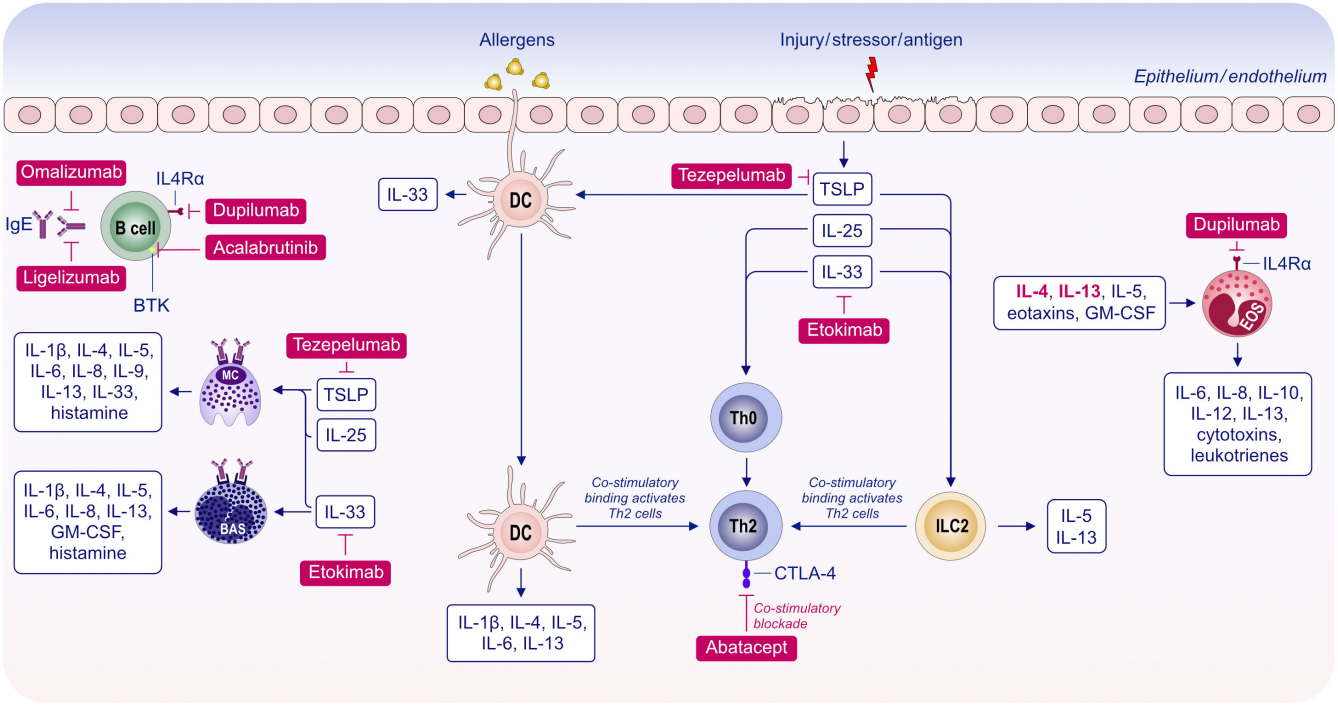

FIGURE 3 Biologics such as anti-IgE antibodies (omalizumab and ligelizumab), anti-IL4Rα antibody (dupilumab), BTK inhibitor (acalabrutinib), anti-IL-33 antibody (etokimab), and anti-TSLP antibody (tezepelumab) have been developed to target key cells and pathways to block the allergenic cascade. Key immune cells targeted include Th2 cells, B cells, mast cells, basophils, dendritic cells, ILC2s, and eosinophils

SU.[98,101] Dupilumab, an IL-4Rα antibody, blocks downstream signaling of both IL-4 and IL-13, key mediators involved in the promotion of B cell IgE class-switching, macrophage polarization toward the pro-inflammatory M2 phenotype, and the induction of peripheral and esophageal eosinophilia.[103] With potential benefits over anti-IgE therapy through broader inhibition of inflammatory pathways, multiple phase II clinical trials are currently evaluating the use of dupilumab for FA. These include trials investigating its use with and without concomitant peanut OIT for PA, as well as the MAGIC study evaluating its use as an adjunct to cow's milk OIT for milk-allergic patients (Table 1). In a first-of-its-kind trial, the COMBINE study, a phase II multi-center trial, is investigating the combined use of biologics for the first time in FA, aiming to simultaneously target multiple allergenic pathways. In the study, the step-wise use of omalizumab followed by dupilumab during concomitant multi-allergen OIT will evaluate safety and efficacy related to desensitization and the induction of SU.

Upstream of the allergic pathway, the interruption of early signaling pathways involving an alarmin, IL-33, with etokimab has shown modest promise in a pilot study.[104] A single dose of etokimab improved desensitization in peanut allergic patients in a DBPCFC 15 days after treatment (73% of patients tolerated 275 mg peanut vs 0% placebo). Beyond each of the biologics present here, trials investigating strategies aimed at novel targets continue to emerge at a consistent pace. A recent example includes a Bruton tyrosine kinase inhibitor (Acalabrutinib).[105]

While the use of biologic therapies aimed to selectively inhibit or modify components of the allergic pathway with or without concomitant allergen exposure, an alternative therapeutic strategy centers on allergen exposure in ways that promote desensitization while avoiding recognition by allergic mediators altogether. Studies investigating the safety and efficacy of intravenously delivered nanoparticle-encapsulated purified peanut extract (CNP-201) are currently underway for those with PA (Table 1). By shielding the peanut antigen from recognition by IgE and other mediators within a nanoparticle matrix, investigators aimed to prevent allergic reactions while the allergen is in circulation and present allergen to naïve T cells in a tolerogenic environment in the liver and spleen.

3 | TECHNOLOGICAL ADVANCES

In addition to ongoing clinical trials, advances in technology are slowly reshaping clinical practice and FA management. The recent COVID-19 pandemic has accelerated the adaptation of remote communication technology to the clinic, and now telehealth consultations are offered by many medical providers.[106-108] Similarly, there are now a variety of phone apps that allergic individuals can use to find allergen-safe food. In the future, apps could be developed to help allergic individuals maintain adherence to daily maintenance OIT and effectively capture associated adverse events for more streamlined communication with medical team. Technologies such

BOX 2 Future research perspectives

- Additional diagnostic tools and techniques to better distinguish true food allergy from sensitivity without clinical allergy.
- Endotyping of disease to fully understand the mechanisms behind development of food allergy and long-term outcomes (natural tolerance vs. persistence).
- A uniform approach to the characterization of reactions during food challenges.
- Standardized grading scales to assess adverse events allowing for the aggregation of challenge outcomes across diverse locations and participants.
- Broadened efforts to characterize underlying mechanisms to allow for targeted biologic interventions.
- Ongoing evaluation of the critical timing of interventions to address skin barrier dysfunction and allergen intake to prevent development of food allergy
- Additional clinical trials to assess the role of probiotics for improved safety with oral immunotherapy.

as virtual and augmented reality have helped to reduce anxiety and fear during stressful procedures such as dental surgery,[109] and pilot studies have started to apply this technology to FA to reduce the stress of OFCs[108] (Box 2).

4 | CONCLUSION

In the face the rising prevalence of FA, the need for improvements in diagnostics, preventative strategies, and therapies remains pressing (Figure 4). Consistent efforts are underway to better understand the mechanisms driving and maintaining FA (Table 2), as well as how these mechanisms vary across the individual, in hopes of designing better interventions for existing FA and its prevention. Built upon a foundation of clinical trials demonstrating the safety, feasibility, and efficacy of both single- and multi-allergen OIT, the field has seen exponential growth in the quantity and variety of innovative therapeutic strategies currently under investigation. Though we await results from many of these pivotal trials, each marks an advancement toward safer therapies that are not only long lasting, but also offer efficacy across the full spectrum of food allergic patients.

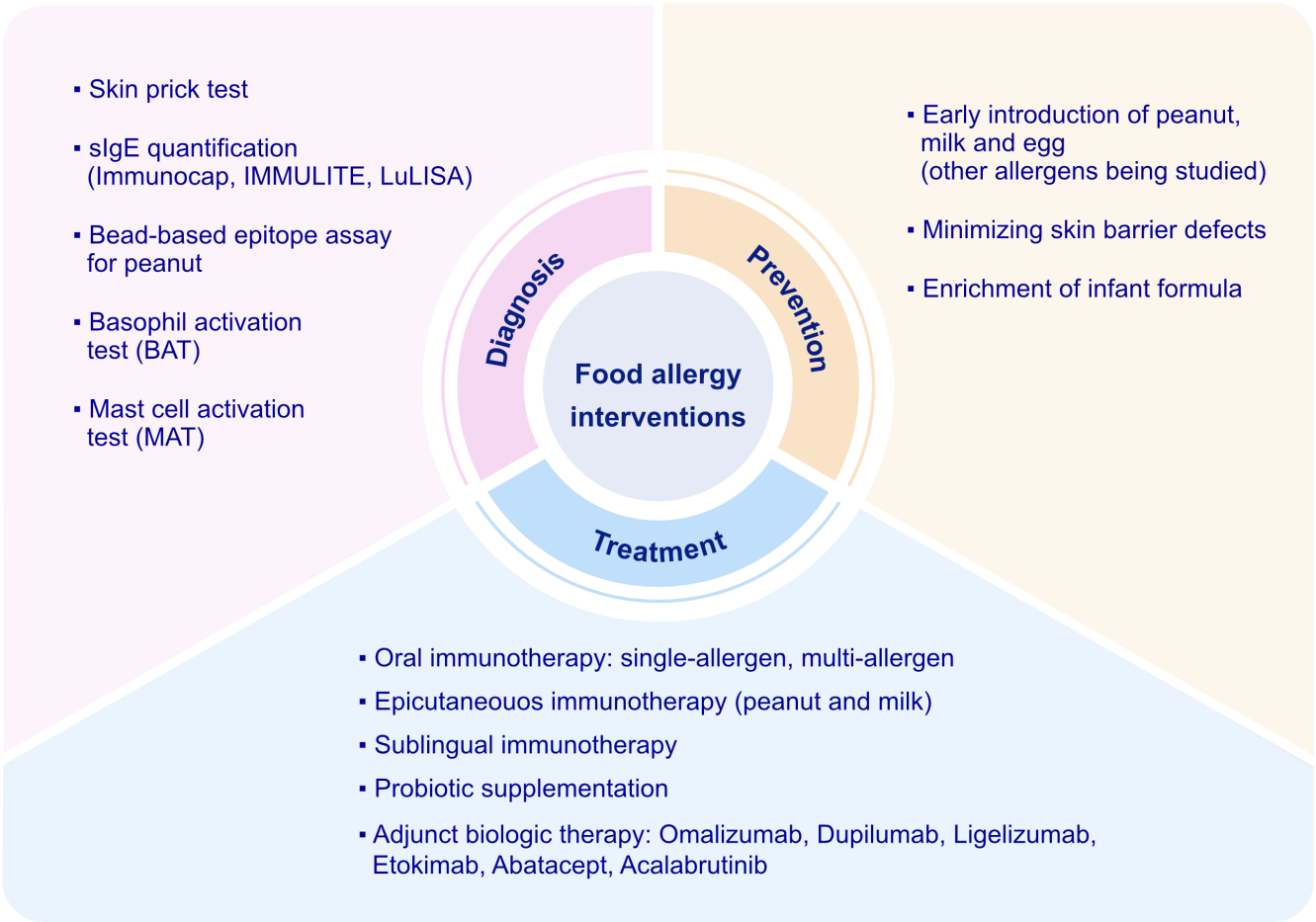

FIGURE 4 In the last few decades, we have made great strides in our understanding of the molecular mechanisms underlying food allergy. These have led to novel diagnostics, prevention strategies, and therapies

TABLE 2 Recent advances in immune modulation in food allergy

Category	Title	PMID	Finding
Antigen-presenting cells	Peanut protein acts as a TH 2 adjuvant by inducing RALDH2 in human antigen-presenting cells	33378690 Ruiter 2020	Ex vivo stimulation of myeloid dendritic cells with peanut protein induced the expression and increased the enzymatic activity of the retinoic acid-production pathway enzyme RALDH2 in a TLR1/TLR2-dependent manner. Co-culture of naive Th cells with peanut protein induced the expression of integrin $\alpha_4\beta_7$ and secretion of IL-5
T cells	Expansion of the CD4 + effector T-cell repertoire characterizes peanut-allergic patients with heightened clinical sensitivity	31654649 Ruiter 2020	The transcriptional profile of $CD154^+$ T cells in peanut sensitive patients favored a polarized TH2 effector phenotype. The ratio of peanut-specific clones in the effector versus regulatory T-cell compartment could distinguish between reactive and hyporeactive patients to peanut
	Immune changes beyond Th2 pathways during rapid multifood immunotherapy enabled with omalizumab	33782956 Manohar 2021	Omalizumab decreased the frequency of IL-4+ peanut-reactive CD4+ T cells, and the expression of GPR15 and CXCR3 frequency in γδ and CD8+ T-cell subsets after 8 weeks. Omalizumab increased several the expression of several genes in CD4+ T cells, CD8+ cell subsets and Th2 effector memory cells
Basophils	Sustained successful peanut oral immunotherapy associated with low basophil activation and peanut-specific IgE	31805311 Tsai 2020	Peanut OIT decreased BAT, peanut s-IgE, and sIgE/total IgE, and increased sIgG4/sIgE. Long term desensitization to peanut required substantial decrease in BAT after OIT
B cells	Origins and clonal convergence of gastrointestinal IgE + B cells in human peanut allergy	32139586 Hoh 2020	Peanut-allergic patients have more diverse IgE isotypes in the stomach, duodenum, and in peripheral blood than non-allergic patients, however the diversity of IgG4 was similar, suggesting that there is an expanded diversity of IgE in food allergy rather than shrinking of the IgG4 pool. Clonal analysis revealed that IgE+ B cells are expanded and somatically mutated in the GI tract, suggesting that the changes in IgE diversity in food allergy stem from the GI tract
	IgE to epitopes of Ara h 2 enhance the diagnostic accuracy of Ara h 2-specific IgE	32248566 Santos 2020	sIgE from peanut allergic patients has higher affinity for seven of the primary peanut allergens, including Ara h 2, than sIgE from peanut sensitive patients. X-ray crystallography showed that these high affinity sIgE peptides are located on flexible regions on the outside of the protein. In contrast to IgE, the binding of IgG4 between peanut sensitive and allergic patients was largely the same, however the ratio of IgG4/IgE was higher in peanut sensitive patients than peanut allergic patients
	Sialylation of immunoglobulin E is a determinant of allergic pathogenicity	32499653 Shade 2020	Peanut allergic patients have increased sialylation of IgE in comparison to non-atopic indivuals. Removal of sialic acid from IgE reduced effector-cell degranulation and anaphylaxis in several allergic model systems.
	High-resolution epitope mapping by AllerScan reveals relationships between IgE and IgG repertoires during peanut oral immunotherapy	34755130 Chen 2021	Peanut allergic patients have several common IgE epitopes in Ara h 1, Ara h 2, Ara h 3, and Ara h 7, 5 of which were present in >70% of patients. These "public" epitopes in peanut allergy patient IgE have several common binding footprints, including a single dominant footprint that is shared by over half the peanut allergic patients. Peanut OIT increases the diversity of IgG but not IgE epitopes and leads to a larger overlap between IgE and IgG binding profiles

CONFLICT OF INTEREST

Dr. Sindher reports grants from NIH, Regeneron, DBV Technologies, AIMMUNE, Novartis, CoFAR, grants and personal fees from FARE, other from Astra Zeneca and DBV; Dr. Long reports consultant fees from COUR Pharmaceuticals; Dr. Nadeau reports gr ants from National Institute of Allergy and Infectious Diseases (NIAID), National Heart, Lung, and Blood Institute (NHLBI), National Institute of Environmental Health Sciences (NIEHS), and Food Allergy Research & Education (FARE); stock options from IgGenix, Seed Health, ClostraBio, and ImmuneID; is Director of the World Allergy Organization Center of Excellence for Stanford, Advisor at Cour Pharma, Consultant for Excellergy, Red tree ventures, Eli Lilly, and Phylaxis, Co-founder of Before Brands, Alladapt, Latitude, and IgGenix; and National Scientific Committee member at Immune Tolerance Network (ITN), and National

Institutes of Health (NIH) clinical research centers, outside the submitted work; patents include, "Mixed allergen composition and methods for using the same," "Granulocyte-based methods for detecting and monitoring immune system disorders," and "Methods and Assays for Detecting and Quantifying Pure Subpopulations of White Blood Cells in Immune System Disorders." Dr. Chinthrajah receives grant support from the Consortium for Food Allergy Research (CoFAR), National Institute of Allergy and Infectious Disease (NIAID), Food Allergy Research & Education (FARE), Aimmune, DBV Technologies, Astellas, Novartis, Regeneron, and Astra Zeneca, and is an advisory board member for Alladapt Immunotherapeutics, Novartis, Sanofi, Allergenis, Intrommune Therapeutics, and Genentech. All other authors indicate no COI.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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