Update 2021: Advances and Highlights in Food Allergy: 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, largescale 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.

Update 2021: Advances and Highlights in Food Allergy: Innovation through a Multi-Targeted Approach

Short title: Food allergy prevention, diagnosis, and treatment

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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, largescale 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.

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] FA additionally presents with significant impacts to quality of life [5,6] and a high economic burden.[7] While the first approved treatment for peanut allergy (PA) is now available,[8]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.[9,10] 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.

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.[11] Recently, LuLISA, an bioluminescent method which requires 1 µL or less of plasma sample has been published.[12] 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.[13]

Beyond IgE characterization, the potential of basophil activation tests (BAT) has been increasingly recognized in recent years.[14,15] However, the effectiveness of BAT differs significantly between allergens [15,16].

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[17]. 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[15]. In addition to a potential role in the diagnosis of FA, BAT may also predict response to OIT.[18] 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 2, Ara h 3, and sIgE/total IgE than those who passed DBPCFCs[19]. 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[20], 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.[21]

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.[22]Ongoing research and novel biomarkers in addition to IgE and basophil/mast activation biomarkers for diagnosis of FA are being developed.[23-26]

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[27], Dribin et al.[28], and CoFAR[29,30], and others[31] 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[32-35]. These tools can assist in diagnostic and treatment strategies in those at risk for the most severe reactions.

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[36-41]. 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%[42]. 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.[43] However, a more recent randomized controlled study found that the introduction of cow's milk formula at 1-2 months reduced the cumulative incidence of milk allergy at 6 months from 6.8% to 0.8%.[44]

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. [45] 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.[46] 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.[47,48]

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[49]. Unsurprisingly, dry skin, as measured by trans-epidermal water loss (TEWL), and atopic dermatitis (AD) have been identified as risk factors for the development of FA[50,51]. Recent evaluation of moisturizers to prevent dry skin and reduce TEWL have presented conflicting results[52-55]; 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[56,57]. In contrast, studies employing moisturizers, such as tri-lipid creams, that do not contain food allergen components and more closely mimic the skin microenvironment have indeed observed reductions in food sensitization[58] accompanied by increases in peanut-specific IgG, decreases in peanut-specific IgE, and a shift towards tolerogenic T cells[52,53]. A multi-center, phase II trial, the SEAL Study (Stopping Eczema and Allergy, NCT03742414), is investigating the efficacy of proactive daily tri-lipid 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.

Therapy

Recent years have witnessed significant developments in the pursuit of safe and effective treatment options for those with FA.[59-61] (**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[8,19,29,60,62-70]. 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 protein in 71% of patients[71]. 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%)[19].

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)[72] and to 444 mg peanut protein in 21.7% of patients after 130 weeks of desensitization[73]. Rates of adherence with EPIT are high (96%) and although reactions are common (77.6%), they are mild and local. [73-75]. 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[76,77]. Peanut SLIT induced desensitization in 25% and SU in 20.8% of patients after 3-5 years of treatment[78]. 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 supports 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[79-81]. 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[82]. 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 [?] 0.001)[83].

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 complex and further research is needed before we can leverage the microbiome 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 [84-86], achieving desensitization to amounts of allergen beyond accidental ingestion (1-2 g protein per food)[87-89]. Compared to placebo, participants receiving adjunct omalizumab prior to and during multi-food 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[87,90-93]. Ligelizumab, another anti-IgE agent with higher binding affinities for free IgE compared to omalizumab, is currently under investigation for peanut allergic patients (NCT04984876)[94-96].

Despite 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[85]. 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 largescale, multi-stage phase III study sponsored by the National Institutes of Health is investigating the use of variable-duration omalizumab therapy for multi-food 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 SU[87,90-93]. 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[97]. 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 (**Table 1**). A single dose of etokimab improved desensitization in peanut allergic patients in a DBPCFC 15 days after treatment (73% of patients tolerated 275mg 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. Some recent examples include a co-stimulatory inhibitor (Abatacept) and Bruton tyrosine kinase inhibitor (Acalabrutinib) (Table 1).

While the use of biologic therapies aims 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 aim 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.

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.

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Box 1: Key findings

Box 2: Future research perspectives

Figure and Table Legends

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.[1-4,98,99]

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.

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.

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 1: Summary of ongoing clinical trials.

+ multi-food oral immunotherapy product

++ nanoparticle-encapsulated peanut protein

§ peanut oral immunotherapy product

Table 2: Recent advances in immune modulation in food allergy.

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Authorship

S.B.S., A.L., A.R.C., and R.S.C. conceived the ideas of the manuscript and prepared the first draft. A.H. designed and revised the Figures. All authors were involved in critical review and revision of the manuscript and approved the final version of the manuscript.

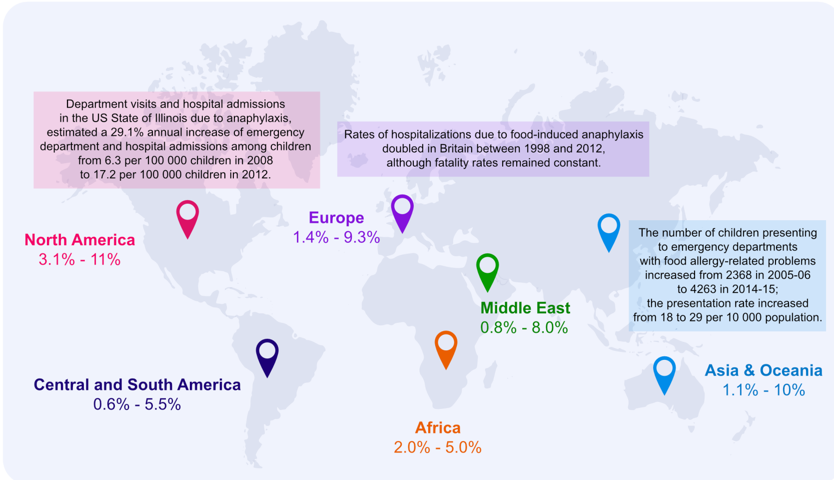

Figure 1_Sindher et al.

	Oral food challenge (OFC)	Skin prick test (SPT)	Allergen-specific IgE	Basophil activation test (BAT)	Mast cell activation test (MAT)	Bead-based epitope assay (BBEA)
Advantages	Gold standard, high sensitivity and specificity	Standardized, fast, cheap	Standardized, high throughput, can be automated	High sensitivity, predictor of response to OIT	Uses plasma which is relatively stable, high specificity	High throughput, high sensitivity and specificity, concordant with OFC results, small blood volume needed
Current limitations	Stressful, time intensive, expensive, high-risk	Poor at distinguishing sensitivity from clinically reactive food allergy	Poor at distinguishing sensitivity from clinically reactive food allergy	Thresholds have not been standardized, usually requires fresh blood, variable specificity	Thresholds have not been standardized, lower sensitivity	Currently only available for peanut, assay development requires molecular characterization of allergens

Figure 2_Sindher et al.

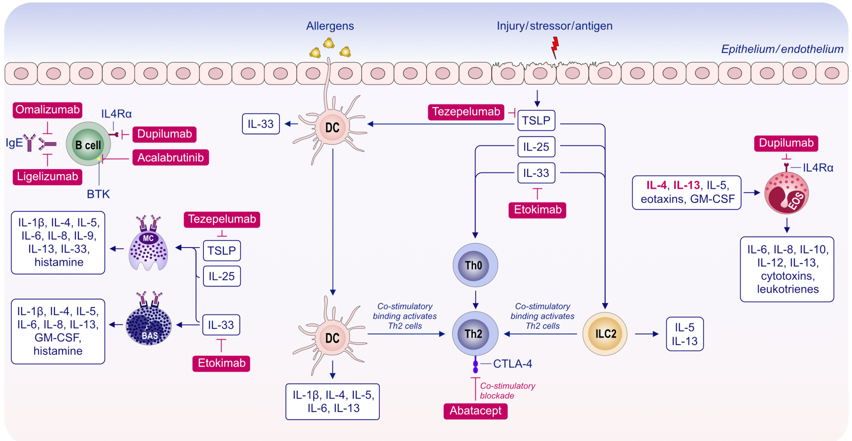

Figure 3_Sindher et al.

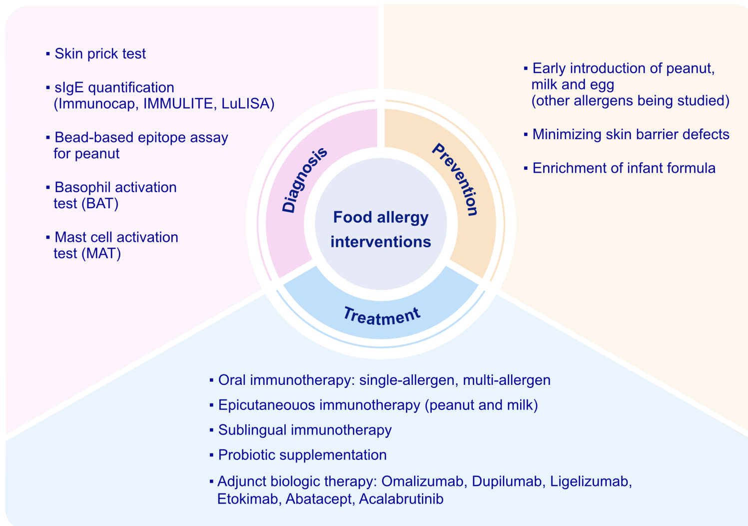

Figure 4_Sindher et al.

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