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Current practices and future trends in cockroach allergen immunotherapy

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ABSTRACT

Purpose of review: This review evaluates the current modes of allergen-specific immunotherapy for cockroach allergens, in terms of clinical outcomes and explores future trends in the research and development needed for a more targeted cockroach immunotherapy approach with the best efficacy and minimum adverse effects.
Summary: Cockroach allergy is an important risk factor for allergic rhinitis in the tropics, that disproportionately affects children and young adults and those living in poor socio-economic environments. Immunotherapy would provide long-lasting improvement in quality of life, with reduced medication intake. However, the present treatment regime is long and has a risk of adverse effects. In addition, cockroach does not seem to have an immuno-dominant allergen, that has been traditionally used to treat allergies from other sources. Future trends of cockroach immunotherapy involve precision diagnosis, to correctly identify the offending allergen. Next, precision immunotherapy with standardized allergens, which have been processed in a way that maintains an immunological response without allergic reactions. This approach can be coupled with modern adjuvants and delivery systems that promote a Th1/Treg environment, thereby modulating the immune response away from the allergenic response.

1. Introduction

Cockroaches are insects that are commonly regarded as pests and are notorious for causing various diseases, including allergies. Among the more than 4000 known species, the American cockroach (*Periplaneta americana*) and German cockroach (*Blatella germanica*), both frequently encountered in indoor environments, play a significant role as allergic sensitizers (Fukutomi and Kawakami, 2021).

Exposure to cockroach allergens has been associated with allergic sensitization (Gold et al., 1999). A study conducted on 476 inner-city children with asthma revealed that children who were both sensitized to cockroach allergens and exposed to elevated levels of these allergens had a higher risk of experiencing increased wheezing frequency, hospitalization, missed school days, and poorer sleep quality compared to those sensitized to other indoor allergens (Rosenstreich et al., 1997). Reducing cockroach infestation has proven to be an effective approach to decreasing cockroach allergen levels (Nalyanya et al., 2009; Rabito et al., 2017; Sever et al., 2007). However, maintaining long-term elimination of cockroaches and their allergens from indoor environments is challenging, making allergen avoidance a difficult task (Brenner et al., 2003; Kinney et al., 2002).

Sensitization to cockroaches has been associated with respiratory allergies, including allergic rhinitis and asthma. Allergic rhinitis is a major risk factor for the development of asthma, with previous studies revealing significant mechanistic overlaps between the two conditions (Bousquet et al., 2015; Liu et al., 2016). According to the ARIA guidelines, management strategies for allergic rhinitis vary based on symptom severity and persistence. These strategies encompass symptomatic relief using pharmacotherapy such as anti-histamines, intranasal corticosteroids, and leukotriene receptor antagonists, either as monotherapy or in combination (Bousquet et al., 2020). Specific allergen immunotherapy (AIT) not only provide long-lasting symptomatic relief and reduces the need for pharmacotherapy, but also modifies the underlying type 2 inflammation mechanism towards a tolerogenic response, thus improving patients' quality of life (Hossenbaccus et al., 2020). Allergen specific immunotherapy is recommended in patients with poorly controlled of allergic symptoms despite pharmacotherapy and allergen avoidance, those experiencing side effects from pharmacotherapy use, or those who prefer to avoid long-term pharmacotherapy use (Bousquet et al., 2021; Hossenbaccus et al., 2020). In addition to its long-lasting benefits, AIT has been shown to prevent the progression of AR to asthma in children (Roberts et al., 2018).

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In this review, we evaluate the existing methods of allergen-specific immunotherapy for cockroach allergens, focusing on their clinical outcomes, and explore future trends in the research and development required to achieve a more targeted approach to cockroach immunotherapy with optimal efficacy, and minimum side effects.

2. Current allergen immunotherapy approaches for cockroach allergy

A search of the present literature reveals that only cockroach extract-based immunotherapy has been evaluated in human clinical trials, while other approaches using defined and purified molecules, such as recombinant allergens, peptides, and DNA vaccines are still at the pre-clinical proof-of-concept stage in animal model studies (Fig. 1).

2.1. Cockroach extracts for AIT

To date, six clinical trials have been conducted using cockroach extracts for immunotherapy (Table 1). The earliest reported trial was by Kang et al. (1988). Patients from this study demonstrated a significant improvement in their symptom and medication scores, accompanied by the presence of functional blocking IgG antibodies (Kang et al., 1988). The second study was a two-year study conducted in India using extracts from the American cockroach (Srivastava et al., 2011). AIT-treated subjects demonstrated a significant reduction in symptoms, and improvement in bronchial hyper-reactivity by the end of the first year of study. By the second year of the study, the reduction in symptoms among AIT-treated patients was correlated to the increase in the IgG4:IgG1 serum antibody ratios, suggesting the role of blocking antibodies in immune-modulation (Srivastava et al., 2011). Wood et al. (2014) next reported a series of four pilot studies aimed to assess the effectiveness of subcutaneous immunotherapy (SCIT) versus sublingual immunotherapy (SLIT) and to assess the presence of adverse effects from cockroach immunotherapy. In general, they reported that the cockroach immunotherapy with extracts were well tolerated, and resulted in the increased of the expected blocking antibodies, and reduced allergy inflammatory responses.

The composition of allergen extracts is prone to variability in its allergen components which is dependent on the quality of the raw material and extraction process (Englert et al., 2021; Mohapatra et al., 2010). Analysis of commercial extracts from German cockroaches demonstrated considerable variability in levels of specific allergens, endotoxin levels, and potency in stimulating T-cell reactivity (Birrueta et al., 2019). Although no tests have been done specifically to evaluate the impact of the differences in composition on the clinical efficacy of immunotherapy, this is very likely given that no immunodominant allergen has been identified among cockroach-allergic individuals (Pomes et al., 2020), and that studies from house dust mite and peanut allergies have also demonstrated that extract composition variability leads to incomplete protective responses against all allergens of a particular source (Chen et al., 2019; Investigators et al., 2018; Uotila et al., 2019).

An additional issue with extracts is the possible presence of contaminating molecules such as endotoxins and microbial proteins that can trigger unwanted immunological responses upon AIT (Dzoro et al., 2018; Glesner et al., 2019). The limitations of an allergen extract may be overcome by the use of purified allergens that can be standardized for their purity and biological activity.

In general, clinical trials of cockroach-extract-based AIT have demonstrated improvements in symptom and medication scores, but adverse reactions have been reported in both SCIT and SLIT delivery systems. Although these adverse effects were mostly classified as mild or moderate events, they remain undesirable outcomes of AIT and can potentially impact patient compliance in completing the treatment course. Adverse allergic reactions occur due to the presence of intact allergens within the AIT extract, which can mount an allergic immune response. One approach to reduce such undesired adverse reactions following AIT is the modification of the allergens to mask, disrupt or remove IgE epitopes while retaining allergen IgG epitope recognition.

Modification strategies have been employed to decrease adverse effects following immunotherapy with allergen extracts from various sources (Jutel et al., 2020; Sola et al., 2018; Sola Martinez et al., 2020). These modified allergens, also known as allergoids, effectively reduce the allergenicity of extracts through allergen polymerization, cross-linking, or denaturation using various methods such as the use of haptens, glutaraldehyde, and polyethylene glycol.

Adjuvants can also be used to alter the immunological response toward allergens. Recently, a pre-clinical trial using mouse models of cockroach allergy was done to assess the efficacy of a combination of cockroach allergen (CRA) mixed with nanoemulsion (NE) mucosal adjuvant via the intranasal route (Baker et al., 2021). Nanoemulsion adjuvants have been identified to suppress the Th2-polarized responses of a typical allergic reaction and skew it towards a Th1 and Th17 phenotype. In this study, cockroach allergen-sensitized mice received three immunizations with allergens coupled to NE. Mice immunized with the CRA-NE vaccine showed reduced airway inflammation and mucus production compared to the control groups (CRA-PBS or NE only). Upon re-challenge with CRA, the CRA-NE treated mice had reduced airway hyperresponsiveness compared to CRA-PBS only. CRA-NE-treated mice had reduced lung IL-12 and ILC2 cells through the suppression of alarmins IL-25 and IL-33. No significant changes in CRA-specific antibodies (IgE, IgG1, or IgG2a), or total CD4, CD8, Treg, or activated Th1 cells were noted between the treatment or control groups. These results suggest that the reduced airway hyperresponsiveness and inflammation are likely driven by ILC2 cells, and can be achieved without humoral involvement (Baker et al., 2021).

While the application of allergoids and adjuvants may seem promising (Baker et al., 2021; Satitsuksanoa et al., 2018), the lack of

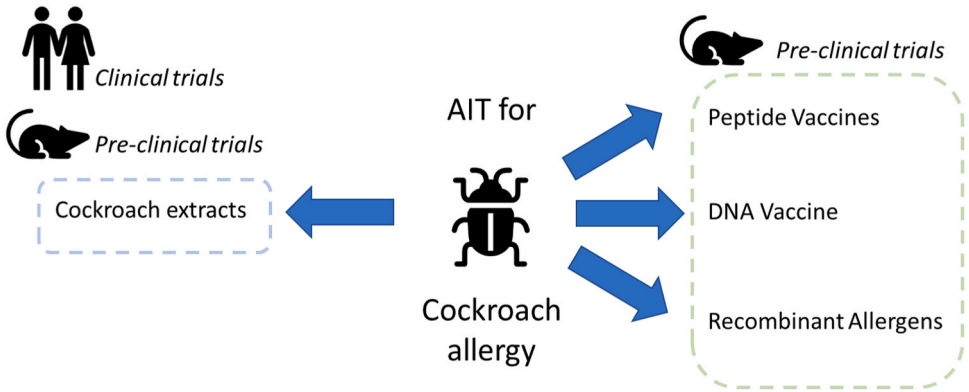

Fig. 1. Different approaches to cockroach allergen immunotherapy (AIT) which has been tested in both human clinical trials and animal pre-clinical trials.

Table 1
Summary of six clinical trials of cockroach immunotherapy performed using cockroach extracts.

No.	Study Design	Main Outcomes
1	Open-label, single-site study Of 28 subjects, 15 were given active treatment (mixed cockroach extract), 13 received a placebo via SCIT. Duration: 60 months.	Individuals from the immunotherapy group showed significant improvement in their symptom scores, and medication scores and demonstrated the presence of blocking IgG antibodies against cockroach extracts and reduced basophil histamine release compared to the control group (Kang et al., 1988).
2	DBPC, single site study. 50 patients with AR, asthma or both, were given American cockroach extract for AIT or placebo for 2 years. Study objective: To assess changes in clinical symptoms, medicine usage and differences in specific biomarkers.	Twenty-four patients in the active group and 18 in the placebo group completed the first year of AIT. The AIT-treated subjects demonstrated a significant reduction in symptoms, improvement in bronchial hyper-reactivity, and an increase in specific IgG4 in comparison to the placebo group. A significant reduction in both medication use and symptoms, a reduction in specific IgE, and an increase in cockroach-specific IgG4 were observed in the treated ($n = 12$) vs placebo group ($n = 18$) after 2 years of AIT. AIT-treated patients also showed a correlation between a reduction in symptom scores and an increase in the IgG4: IgG1 ratio (Srivastava et al., 2011).
3	Open-label, single-site study (SCSS study). 27 subjects (adults and children) with a history of AR were administered German cockroach extracts via SLIT for 14 days. Extracts contained 4.2 μg Bla g 2 and 50 μg Bla g 1. Study objective: To assess the safety of the cockroach allergen extract dose by the number and severity of adverse events.	In the adult group, 7 of 9 participants reported treatment-related adverse events, ranging from oral or throat pruritus ($n = 5$), non-urticarial rash ($n = 3$), and nausea ($n = 1$). In most cases, symptoms were graded as mild, except moderate in 1 patient. In the 8–17-year-old group, 2 participants suffered from oral pruritus' which resolved upon antihistamine treatment. In the 5–7-year-old group, three participants reported mild reactions to the immunotherapy (nasal congestion, pruritus of the nose and eyes and facial hive, and erythema on the neck (Wood et al., 2014).
4	DBPC, multicentre study (BioCSI study). 54 adult subjects with a history of AR were administered German cockroach extracts via SLIT for 6 months. Extracts contained 4.2 μg Bla g 2 and 50 μg Bla g 1. Study Objective: To determine changes in cockroach-specific IgE levels between treatment or placebo groups.	The immunotherapy group had an almost 2-fold increase in specific IgE compared to placebo ($p < 0.0001$), and a trend towards an increase in IgG4 responses. The blocking antibody responses did not differ significantly between both groups (Wood et al., 2014).
5	DBPC, multicentre, low and higher dose study (BioCSI2 study). 99 subjects (children) were enrolled, including 30 in the high-dose group (16.8 μg Bla g 2, 202 μg Bla g 1), 31 in the low-dose group (4.2 μg Bla g 2, 50 μg Bla g 1), and 28 in the placebo group. Duration: 3 months Study objective: To determine changes in cockroach-specific IgE levels between high/low treatment or placebo groups.	Significant differences between the levels of specific IgE, IgG, and IgG4 were found between the treatment and placebo groups. However, the levels of these serological markers did not differ significantly between the low-dose and high-dose treatment groups (Wood et al., 2014).
6	Open-label, single-site study (SCITCO study). 10 adult subjects with cockroach sensitization and AR, asthma, or both were given German cockroach extracts as immunotherapy. Extracts contained 6 μg of Bla g 2 and 120 μg of Bla g 1. Duration: 6 months. Study objective: To assess the safety of the cockroach allergen extract dose by the number and severity of adverse events.	Throughout this study, 147 mild adverse events, and 3 moderate adverse events were reported, but none required adjustments in dosing. There was a significant increase in cockroach-specific IgE and IgG_4 levels, as well as inhibition of facilitated antigen binding activity compared to baseline (Wood et al., 2014).

standardization for the composition of the resulting modified product, coupled with the difficulties in standardizing the initial allergen extract preparation poses serious challenges to the reproducibility of this approach for clinical applications (Zimmer et al., 2017).

2.2. Recombinant cockroach allergens for AIT

The advancement of genetics and molecular tools made it possible to clone individual allergens and prepare highly purified recombinant allergens from cockroaches which allows for detailed immunological characterization. The understanding of cockroach allergens at a molecular level started in 1995, with the cloning of Bla g 2 (Arruda et al., 1995), the allergen database currently reports the identification of 20 allergens from *P. americana* and 11 allergens from *B. germanica*, each belonging to unique protein families (Table 2).

As previously mentioned, allergen extract preparations are difficult to standardize, which results in variable AIT outcomes. The use of recombinant allergens can overcome the limitations of allergen extracts while enabling the preparation of allergens with high purity in a reproducible manner to provide consistent and reproducible outcomes (Tscheppe and Breiteneder, 2017).

Table 2
Identified cockroach allergens from *Periplenata americana* and *Blatella germanica* as reported in the allergen database (www.allergen.org).

Allergen group	Biochemical Name	Molecular Weight (kDa)	Cloned allergens
1	Nitrile specifier, microvilli-like protein with unknown function	46	Per a 1, Bla g 1
2	Aspartic protease-like and inactive aspartic protease-like	42	Per a 2, Bla g 2
3	Arylphorins/TO Arthropod hemocyanins	72	Per a 3, Bla g 3
4	Lipocalin	17	Per a 4, Bla g 4
5	Glutathione S-transferase	23	Per a 5, Bla g 5
6	Troponin C	17	Per a 6, Bla g 6
7	Tropomyosin	33	Per a 7, Bla g 7
8	Myosin light chain	22	Per a 8, Bla g 8
9	Arginine kinase	43	Per a 9, Bla g 9
10	Serine protease	28	Per a 10
11	Alpha amylase	55	Per a 11, Bla g 11
12	Chitinase	45	Per a 12, Bla g 12
13	Glyceraldehyde-3-phosphate dehydrogenase	36	Per a 13
14	Enolase	50	Per a 14
15	Cytochrome C	15	Per a 15
16	Cofilin	20	Per a 16
17	Alpha-tubulin	53	Per a 17
18	Peptidyl-prolyl-cis-trans isomerase; Cyclophilin	24	Per a 18
19	Porin 3	7.4	Per a 19
20	Peroxiredoxin-6 (Prx6)	24	Per a 20

Relatively few studies have been done to assess the effectiveness of recombinant cockroach allergens for AIT, and all studies are at the pre-clinical stage. The first study conducted in 2010 evaluated the efficacy of recombinant Per a 10 as an AIT molecule in a mouse model of cockroach allergy sensitized using cockroach extract (Srivastava et al., 2010). Reduction in specific serum IgE levels, and reduction in inflammatory responses as seen in reduced lung infiltration with eosinophils and decreased IL-4 cytokine levels in the bronchoalveolar lavage (BAL) fluids. The use of proteolytically inactive Per a 10 as an immunotherapy molecule resulted in more substantial reductions in the levels of specific serum IgE, which was accompanied by higher IL-10 secretion in the BAL fluids, and eosinophilic infiltration in the lung (Srivastava et al., 2010). Nevertheless, the authors reported that the IgG1 and IgG2a levels did not show differences pre-and post-IT, which brings into question the role of blocking antibodies in this IT model.

The arginine kinase allergen of *P. americana*, Per a 9 was also evaluated for its effectiveness as an AIT molecule in two studies (Prangtaworn et al., 2018, 2021). Immunotherapy of cockroach-sensitized mice with liposome-encapsulated Per a 9 induced higher expression of IFN-γ, reduced Th2 gene expression (IL-5, IL-13) in lung tissues and reduced lung inflammation compared to treatment with liposomes alone (Prangtaworn et al., 2018). The authors further evaluated a combination of Per a 9 with two distinct Tregitopes (T289 and T167) encapsulated in liposomes as AIT molecules. Tregitopes are epitope peptides that can stimulate regulatory T-cell expansion. Mice treated with liposome encapsulated Tregitopes and Per a 9 demonstrated reduced lung inflammation compared to placebo but did not differ from treatment with Per a 9-liposome alone. In addition to the suppression of Th2 genes (IL-4, IL-5, IL-13), Tregitope-Per a 9-treated mice additionally had increased expression of cytokine genes (TGF-β, IL-10, and IL-35 for L-T289-Per a 9, and TGF-β and IL-10 for L-T167-Per a 9), indicating the action of these AIT molecules in promoting T-regulatory responses, while suppressing Th2 responses in this animal model (Prangtaworn et al., 2018).

The same research group later evaluated a liposome preparation containing Per a 9 and a TGF-β homologue (TGH) for the nematode *Brugia malayi* as a potential AIT molecule (Prangtaworn et al., 2021). TGF-β homologue from *B. malayi* has been demonstrated to increase the number of regulatory T cell subtypes that downregulate host immune responses upon infection (Metenou and Nutman, 2013). The therapeutic effects of liposome-Per a 9 alone, liposome-TGH alone, and liposome-TGH with Per a 9 were evaluated. All three vaccine preparations were able to reduce the type-2 helper T cell responses in the cockroach-sensitized mice model, however, the underlying mechanisms seemed to differ. The use of Per a 9 encapsulated in liposome demonstrated an increase in IFN-γ gene expression compared to placebo control, while the introduction of TGH (either TGH-liposome, or TGH-Per a 9-Liposome) showed a down-regulation of IFN-γ expression, and upregulation of immunosuppressive cytokine gene expression (IL-10, TGF-β), indicating a regulatory T cell response (Prangtaworn et al., 2021).

At present, the use of recombinant allergens for cockroach AIT is still at the proof-of-concept level, as no major cockroach allergen has been determined, unlike in dust mite, cat, or peanut allergy, where AIT against the major allergen alone is deemed sufficient to treat these conditions. Nevertheless, the few studies done using recombinant cockroach allergens as AIT molecules have indicated the promotion of Th1 and Treg responses, in line with the expected immune modulatory effects of AIT.

3. Modified cockroach allergens for AIT

3.1. Cockroach allergen T-cell peptide epitopes for AIT

Recombinant allergens may still harbor certain limitations, as the presence of intact IgE epitopes could initiate unwanted allergic responses when used as an immunotherapy molecule. The use of defined peptides that stimulates T-cell responses, without the presence of IgE epitopes is one way to overcome this limitation. In addition, the use of T-cell epitope-derived peptides has shown to be efficacious and safe in previous research undertaken for allergies against other common indoor and outdoor allergens (Huang et al., 2019; Moldaver et al., 2019; Simms et al., 2015).

Sharma et al. investigated the effects of three peptides containing T-cell epitopes of Per a 5 as AIT molecules (Sharma et al., 2022). Immunotherapy with all three T-cell epitope peptides of Per a 5 (TC-P1, TC-P2, and TC-P3) in cockroach-sensitized mice model resulted in increased levels of immunoregulatory molecules and downregulation of NF-κB signaling in the lung (Sharma et al., 2022). Individual peptides also demonstrated unique immune mechanisms in AIT treatment. Treatment with TC-P3 resulted in a three-fold reduction of cellular infiltration of the lung compared to the placebo control. TC-P2 and TC-P3 caused a reduction of specific IgE, an increase in IgG2a levels, and a reduction in Th2 cytokine levels as compared to placebo control. TC-P1 and TC-P2 treatment showed an increase in $CD4^{+}FoxP3^{+}$ T regulatory cells.

3.2. DNA vaccines for cockroach AIT

Immunization using plasmid DNA encoding for an allergen mimics a viral infection, where host cells are transfected to produce allergen proteins in situ. As the foreign antigen is now intracellular, it stimulates the immune activation of T-helper 1 and T-regulatory cells that counteract the primarily Th2 response in a classical allergic response (Scheiblhofer et al., 2018). Zhou et al. (2012a) investigated the therapeutic potential of a DNA vaccine encoding for Bla g 1 in a mouse model sensitized with Bla g 1 allergen having airway inflammation.

In the prophylactic experiments, naïve mice were given three doses of Bla g 1 DNA vaccine, followed by Bla g 1 sensitization and challenge. Mice in this group showed significantly lower specific IgE levels and reduced levels of IL-4 and IL-5 cytokines infiltrating eosinophils in the BAL fluids. In the therapeutic experiments, Bla g 1 sensitized mice were three doses of Bla g 1 DNA vaccine, followed by a challenge with Bla g 1. Similar to observations in the prophylactic experiments, Bla g 1 DNA vaccination resulted in significantly reduced serum IgE levels against Bla g 1, almost undetectable levels of eosinophils in the lungs, and correspondingly the levels of IL-4 and IL-5 in BAL were significantly reduced compared to control. In addition, therapeutic vaccination was able to induce IL-10-secreting Treg cells. Vaccination with Bla g 1 additionally reversed an established airway inflammatory state to a non-inflammatory state (Zhou et al., 2012a).

Zhou and colleagues also investigated the application of Bla g 2 DNA vaccination for its prophylactic potential (Zhou et al., 2012b). Bla g 2 DNA vaccination decreased the levels of specific IgE in serum, and allergen-induced lung inflammation in mice upon challenge with Bla g 2, demonstrating the protective effect of prophylactic DNA vaccination (Zhou et al., 2012b).

4. Future trends in cockroach AIT

4.1. Precision diagnosis

The current clinical diagnosis for cockroach allergy is based on the use of cockroach extracts. The poor reproducibility of allergen extract preparation impacts the diagnostic outcomes (Birrueta et al., 2019; Valenta et al., 2018). In addition, cockroach diagnosis via skin prick test or specific IgE tests are often performed using extracts of a mixture of cockroach species, making it complicated for the clinician to identify the specific cause of the allergic reaction(s).

Prior research has pointed to two main characteristics among cockroach allergen-sensitized individuals. First, the dominant/ major cockroach allergen has not been determined (Glesner et al., 2019; Pomes et al., 2020). In other allergen sources where immunodominant allergens have been identified, such as dust mites (Der p 1, Der p 2), birch

pollen (Bet v 1), and grass (Phl p 5), these dominant allergens are used to standardize the concentrations of allergen extracts. Given that the majority of allergic individuals would react to the immunodominant allergen, this strategy has mostly worked for extracts from these sources, as reflected by successful AIT trial results (Moingeon et al., 2016; Wurtzen et al., 2016; Yang and Zhu, 2017). However, this is not the case for cockroach allergens. The lack of an immunodominant cockroach allergen signifies a greater need for precision diagnosis to identify the sensitizing allergenic component. Precision diagnostics (Fig. 2) can now be made possible as the efforts in molecular characterization of cockroach allergens have uncovered at least 20 unique cockroach allergens (Tables 1 and 2). Patients with a convincing clinical history of cockroach allergy, and a positive skin prick test can be further diagnosed using component-resolved diagnosis to identify the precise offending allergen molecule(s). The use of technology such as allergen chips has enabled the ease of reliable diagnosis of multiple purified allergens (Lupinek et al., 2014).

The second characteristics of cockroach-allergic individuals are that they are often polysensitized to other allergen sources. Among the more common sources are dust mites and crustaceans, which are thought to be due to the presence of cross-reacting allergens such as tropomyosin and arginine kinase. Based on the 20 biochemically unique cockroach allergens identified, the presence of similar allergens in other sources may point to a larger possibility of cross-reactivity that has yet to be researched (Table 3). This opens up a new opportunity for therapeutic intervention, that is based on the molecular allergen structure, rather than the source of allergen. For example, an individual who is primarily sensitized to cockroach-tropomyosin, and cross-reacts to tropomyosin allergens from dust mites and shrimp could be given tropomyosin-specific immunotherapy. This strategy will likely increase the efficacy of immunotherapy, due to the treatment with standardized doses of purified tropomyosin in the AIT regiment.

4.2. Wild-type and modified allergens for AIT

4.2.1. Recombinant allergens

As described in the earlier sections of this review, two cockroach allergens, Per a 9 and Per a 10 have been assessed as immunotherapy molecules in mice models of cockroach allergy (Prangtaworn et al., 2018, 2021; Srivastava et al., 2010). Although 18 other allergen groups have been identified, they have yet to be tested as AIT molecules. In comparison to the development of AIT in other allergen sources, research interest in cockroach allergens is relatively recent. Hence, data from immunotherapy experiments and trials involving other allergens, particularly respiratory allergens may serve as a good reference point for the future development of cockroach AIT approaches.

4.2.2. Hypoallergens

While recombinant allergens can be prepared with high purity, and with defined biological activity, it still has the limitation of inducing an IgE-mediated adverse event in AIT, due to the presence of intact IgE epitopes. To overcome this, recombinant allergens may be genetically engineered, chemically modified or heat-treated to reduce or abolish their IgE binding capacity. Hypoallergic molecules generated using the genetic engineering approaches have demonstrated positive results in pre-clinical and early-phase clinical trials in a wide range of allergens when used as AIT molecules (Klimek et al., 2015; Tscheppe et al., 2020; Zuidmeer-Jongejan et al., 2015).

Glycation, a process where sugars are covalently attached to an allergen, may destroy or mask IgE epitopes of allergenic proteins, resulting in an allergen with reduced IgE binding capacity. Recently, Zhang and colleagues investigated the applicability of glycated purified shrimp tropomyosin (Pen a 1) as a potential immunotherapy molecule using a tropomyosin-sensitized mouse model (Zhang et al., 2021). They identified that glycated Pen a 1 had reduced allergenicity as demonstrated by reduced specific IgE and increased specific IgG2a levels, lower mast cell activation, downregulation of Th2 cytokines, upregulation of Treg and Th1 cytokines post immunotherapy (Zhang et al., 2021). Given the high sequence similarity and potential cross-reactivity between tropomyosins of different origins (Table 3), glycation of cockroach tropomyosin could be considered as a route for hypoallergen development.

Regardless of the method of allergen modification, care must be taken to ensure that modifications to the wild-type allergen result in reducing or abolishing the IgE-binding capacity, while still maintaining the IgG epitopes and the T-cell epitopes that are vital for the immune modulation of allergic responses (Akinfenwa et al., 2021).

4.2.3. T and B cell epitope peptides

Besides systematic targeting and removal of IgE epitopes from allergen molecules, other forms of hypoallergenic molecules are T- and B- cell epitope peptides. T cell epitope peptides encompass linear epitope regions that are able to activate T cell proliferation while lacking any IgE epitope sequences. Immunization with T cell epitope peptides would induce a T cell tolerance response that can be further characterized as suppression of allergen-specific T cell proliferation and the subsequent cytokine responses, and generation of allergen-specific T regulatory cells (Akdis and Akdis, 2007). Suppression in T cell responses

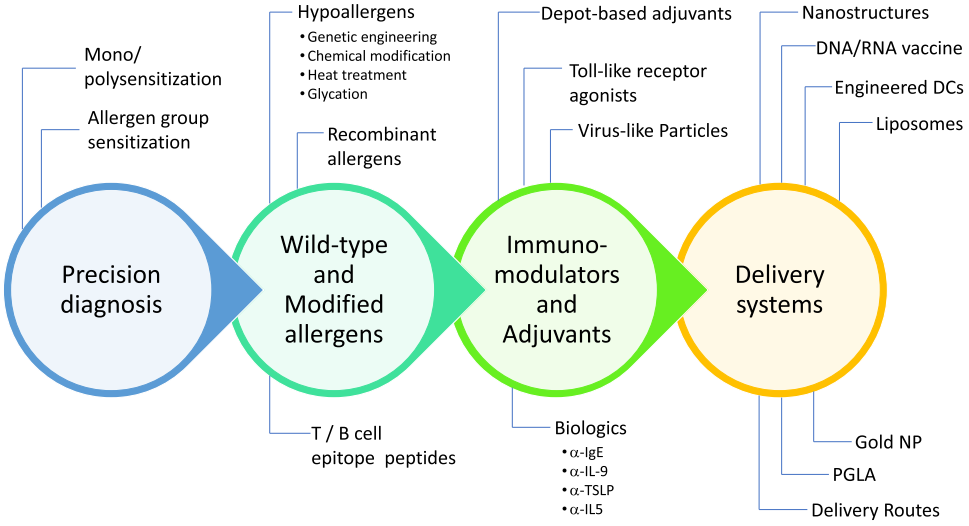

Fig. 2. Future trends in cockroach allergen-specific immunotherapy.

Table 3
Biochemical grouping of cockroach allergens, and the potential cross-reactive allergens from other sources.

Allergen Group	Reference Cockroach Allergen (s)	Other sources (Potentially cross-reactive)								
		Insect	Dust mite	Crustacean	Mollusc	Fish	Nematode	Mammals	Fungus	Others
Nitrile specifier	Per a 1, Bla g 1									
Aspartic protease	Per a 2, Bla g 2									
Hemocyanin	Per a 3, Bla g 3			x						
Lipocalin	Per a 4, Bla g 4							x		
Glutathione S-transferase	Per a 5, Bla g 5		x				x		x	
Troponin C	Per a 6, Bla g 6		x	x						
Tropomyosin	Per a 7, Bla g 7	x	x	x	x	x	x			
Myosin Light Chain	Per a 8, Bla g 8		x	x				x		Chicken
Arginine kinase	Per a 9, Bla g 9	x	x	x	x	x				
Serine protease	Per a 10	x							x	Muskmelon
Alpha amylase	Per a 11, Bla g 11		x							Barley
Chitinase	Per a 12, Bla g 12									Chestnut, coffee, mango, banana, avocado, pomegranade, chinese date, maize, latex
Glyceraldehyde-3-phosphate dehydrogenase	Per a 13					x				Wheat
Enolase	Per a 14					x			x	Grass, Chicken, Latex, Ragweed, Wormwood
Cytochrome C	Per a 15								x	
Cofilin	Per a 16		x							
Alpha-tubulin	Per a 17		x							
Peptidyl-prolyl-cis-trans isomerase; Cyclophilin	Per a 18		x						x	Peanut, Birch, Olive, Tomato, Rosy periwinkle
Porin 3	Per a 19	x								
Peroxiredoxin-6 (Prx6)	Per a 20									

leads to the reduction of specific IgE production and inflammatory responses (Larche, 2011). As previously mentioned, one study has been published on the efficacy of T-cell epitope peptides of the group 5 cockroach allergen as an AIT molecule with promising outcomes (Sharma et al., 2022).

The use of B-cell epitope peptides for AIT focuses on IgG epitopes that can induce the production of allergen-specific blocking IgGs. As antibody production is dependent on T-cell help, B-cell peptides must be supplemented with a non-allergenic T-cell peptide. B-cell epitopes of several cockroach allergens have been identified (Lee et al., 2015; Sookrung et al., 2014; Sookrung et al., 2018), however, its utility in AIT remains to be explored. One B-cell epitope peptide-based study that has advanced to early clinical trial stages is that of grass pollen allergen. Construct BM32 consists of non-allergenic B-cell epitope peptides of four grass pollen allergens (Phl p 1, Phl p 2, Phl p 5, and Phl p 6) which is fused to an immunogenic carrier protein that provides the T-cell help (Focke-Tejkl et al., 2015). This peptide was able to stimulate the production of allergen-specific blocking IgG antibodies, while not stimulating any allergen-specific IgE responses (Zieglmayer et al., 2016).

Both T- and B-cell epitope peptides are potential strategies to be explored for the development of cockroach AIT. The advantage of synthetic peptides is the reproducibility of their production, low production cost, and stability in the lyophilized form that does not require cold storage (Moldaver and Larche, 2011).

4.3. Immunomodulators and adjuvants

4.3.1. Alum and other depot-based adjuvants

Aluminium salts have been used for allergen immunotherapy for almost 100 years and are the dominant adjuvant used today. It has a dual role in vaccination. First, it acts as a depot (reservoir) of the antigen, allowing for slow release of the antigen from the site of the injection, hence prolonging the stimulation of the immune system (Heine et al., 2022). The gradual release of allergens reduces the risk of anaphylaxis response, hence increasing the safety profile of AIT (Jensen-Jarolim, 2015). Second, aluminium salts promote a Th2 response (Marrack et al., 2009; Reed et al., 2013), which is similar to that of an allergic response. In AIT, the immune response should be modulated away from Th2 towards a tolerogenic response that favors the regulatory T cell or Th1 pathways (Lundberg et al., 2016). Therefore, the use of aluminium salts limits the efficacy of AIT. This has encouraged the research of different adjuvant molecules that have the depot effect, while able to stimulate Th1 responses and are biodegradable.

Newer adjuvant molecules which are biodegradable and with Th1 stimulating capacities such as microcrystalline tyrosine (MCT), monophosphoryl lipid A (MPL) and hydrogel polymers are now being tested in both pre-clinical and clinical studies (Table 4). The use of adjuvant molecules reduces the duration of AIT and promotes its long-term efficacy beyond the treatment period (Table 4).

4.3.2. Toll-like receptor agonists

Toll-like receptors (TLRs) are membrane-bound sensor proteins that plays a crucial role in innate immune responses by recognizing foreign molecules from microbes and bacteria. Toll-like receptors are expressed on both non-immune and immune cells, and their activation can impact the adaptive immune response through their expression on dendritic cells. Toll-like receptor activation promotes a Th1 environment, which has the potential to facilitate a more rapid onset of the tolerogenic response in AIT (Gerhold et al., 2008; Wang and McCusker, 2006).

Toll-like receptor agonists are substances capable of specifically activating TLRs by mimicking pathogenic molecular patterns, thereby triggering an immune response. Numerous TLR agonists have been tested for their immunomodulatory and adjuvant properties in the context of AIT (Table 5). Generally, these agonists are well-tolerated and promote a Th1 and/or Treg response. Recent research in the area of TLR agonist adjuvants has been focused on improving the safety profile and stability of these molecules. Modified adjuvant molecules with reduced toxicity such as MPL and polyadenylic:polyuridylic acid (poly A:U) compared to their predecessors (lipopolysaccharide, LPS, polyinosinic: polycytidylic acid (poly I:C) respectively) and are being evaluated for adjuvants with better safety profiles (Kirtland et al., 2020). CpG ODNs at high concentrations demonstrate both adjuvant and toxic properties. The co-delivery of CpG-ODNs with a depot matrix such as hydrogels, liposomes or nanoparticles, offers the advantage of controlled release

Table 4
Clinical and pre-clinical trial outcomes in AIT approaches of selected studies employing adjuvants.

Adjuvant type	Composition	Outcomes in AIT	Ref
Aluminium salts	Alum-conjugated grass pollen (*Phleum pratense*) extract	AIT treatment with alum-conjugated grass pollen extract improved the quality of life of AR patients during the pollen season.	(Powell et al., 2007)
Microcrystalline tyrosine (MCT)	Crystalline form of L-Tyrosine-Fel d 1	MCT induced lower IL-4 secretion compared to Alum, with fewer anaphylactic reactions among the immunized mice. Specific IgG production was comparable between MCT and alum.	(Leuthard et al., 2018)
	MCT-Der p allergoid	Dermatophagoides-sensitized asthmatic patients treated with Acarovac Plus ® showed a reduction in medication need and symptomatic days. Significant improvements in asthma-related QoL were recorded 6- and 12 months post-treatment.	(Padro et al., 2022)
MCT-MPL	MCT with 3-deacyl-monophosphoryl lipid A-coupled with allergoids of pollen extracts	AIT with Pollinex Quatro specific to olive and olive/grass pollens lowered the use of asthma medication, and reduced hospital visits, suggesting the efficacy of this treatment.	(Florido-Lopez et al., 2020)
	MCT-MPL-*Phleum pratense* allergoid	Improvement of clinical symptoms (running nose, sneezing, conjunctivitis and the weekly overall score) was observed in the MPL-AIT group compared to the control group, among patients who have stopped the immunotherapy 3–6 years prior, demonstrating the long-term effects of the therapy.	(Zielen et al., 2018)
Hydrogel	PLGA-PEG-PLGA-OVA	Outcomes of AIT delivered with or without hydrogel in an OVA-sensitized mouse model showed no significant differences in the reduction of Th2 cytokines and the reduction of sIgE. The hydrogel-AIT group showed higher levels of sIgG1 compared to AIT alone, possibly due to the depot effect.	(Heine et al., 2022)

Table 5
Clinical and pre-clinical trial outcomes in AIT approaches of selected studies employing Toll-like receptor agonists.

Location	Toll Like Receptor (TLR)	TLR Agonist	Main Findings
Extracellular	TLR2/1	Pam3CSK4	Peripheral blood mononuclear cells from allergic patients who received 1 year of Der p AIT showed increased CD137 expression on CD8 +CD25 + T cells compared to pre-immunotherapy. CD137 is a co-inhibitor for Th2 differentiation. In vitro stimulation with Pam3CDK4 further enhanced the CD137 expression, which subsequently increased the production of IL-10, and decreased the production of IL-4 (Tsai et al., 2019).
	TLR2/6	Macrophage-activating lipopeptide 2 kDa (MAPL-2)	Human monocyte-derived DC from allergic patients pulsed with allergen and co-cultured with autologous lymphocytes resulted in increased IL-4 and decreased IFN-γ secretion in vitro. Stimulation of the allergen-pulsed DCs with MAPL-2 and IFN-γ resulted in > 50-fold increase in IFN-γ production compared to co-cultures with allergen alone, and a concurrent increase in the proliferation and the number of IFN-γ producing lymphocytes, indicating a skew towards a Th1 response post-treatment (Weigt et al., 2004).
		Bisacyloxypropylcysteine polyethylene glycol conjugate (BPPcysMPEG, MALP-2 derivative)	Immunotherapy treatment of mice sensitized with the Timothy grass pollen extract co-administered with MAPL-2 derivative resulted in reduced infiltration of eosinophils and attenuation of IL-4 and IL-5 levels in the BALF. The AIT with MAPL-2 derivative was able to rebalance the initial allergic Th2 skewed response (Fuchs et al., 2010).
	TLR4	Monophosphoryl-lipid A (MPL)	Pollinex® preparations involved adjuvanting olive/olive + grass extracts with MPL and adsorbing them to L-

(*continued on next page*)

Table 5 (*continued*)

Location	Toll Like Receptor (TLR)	TLR Agonist	Main Findings
			tyrosine. Patients with allergic asthma treated with Pollinex® olive or Pollinex olive/grass had lower medication use, and lesser visits to healthcare centers compared to the non-AIT treatment group (Florido-Lopez et al., 2020). In a placebo-controlled phase IIb study, MPL adjuvanted ragweed allergoid adsorbed to L-Tyrosine was used in AIT that was given over 4 injections before the ragweed season. The AIT group showed reduced allergy symptoms in patients with seasonal allergic rhinitis compared to the placebo group and was well tolerated (Patel et al., 2014).
		Glucopyranosyl lipid A (GLA)	Cry j 1 sensitized mice were treated with Cry j 1 with or without GLA adjuvant via SCIT, followed by intranasal challenge with JC pollen extract. Cry j 1-GRA treated mice demonstrated suppression of sneezing following intranasal challenge and reduced eosinophil infiltration in the nasal lavage fluid and nasal epithelium. In vitro co-culture of $CD11c^+$ DC with $CD4^+$ T cells from spleens of Cry j 1-GRA treated mice resulted in lower IL-5 secretion, and increased IFN-γ and IL-10 production compared to non-adjuvanted AIT (Matsumoto et al., 2020).
	TLR5	Flagellin	Flagellin B from the gram-negative *Vibrio vulnificus*, when expressed as a fusion protein with the major dust mite allergen Der p 2 was able to reduce airway hyperresponsiveness, eosinophilic infiltration and allergen-specific IgE production in a HDM-induced mouse asthma model more effectively than the group treated with a mixture of flagellin and Der p 2 (Tan et al., 2019).

Table 5 (*continued*)

Location	Toll Like Receptor (TLR)	TLR Agonist	Main Findings
			A truncated version of flagellin from Salmonella Typhimurium was expressed as a recombinant protein with the major birch pollen allergen, Bet v 1. When injected in mice, this recombinant protein produced specific blocking antibodies that were able to block patients' serum IgE binding to Bet v 1, and demonstrated a stronger T-cell stimulation compared to Bet v 1 alone (Kitzmuller et al., 2018).
Intracellular	TLR 3	Polyinosinic:polycytidylic acid (poly I:C)	Poly I:C given during OVA-sensitization in mice suppressed the titres of IL-5, lung eosinophil infiltration and airway hyperresponsiveness upon OVA challenge. Poly I:C was also effective in suppressing established asthma in the OVA-sensitized mice model. In addition, poly I:C injection significantly increased the production of IL-10, IFN-γ and IL-12p70 indicating a Th1 and Treg response (Sel et al., 2007).
	TLR3/7	Polyadenylic:polyuridylic acid (poly A:U),	The immune effects of poly A:U were determined in vitro in a bone marrow dendritic cell (BM-DC) culture stimulated with Fms-like tyrosine kinase 3 ligand (Flt3L). BM-DC stimulated with poly A:U produced both IFN-α and IL-12p40. IFN-α stimulation was specific to poly A:U stimulation as it was not observed when poly I:C was used. Furthermore, IFN-α production was linked to the TLR3/TLR7 signaling pathway depending on the subset of DC (Sugiyama et al., 2008).
	TLR7	8-oxoadenine	8-oxoadenine coupled to a T cell peptide of Pru p 3 promoted the maturation of monocyte-derived DCs obtained from PBMCs of Lipid Transfer Protein allergic or

(*continued on next page*)

Table 5 (*continued*)

Location	Toll Like Receptor (TLR)	TLR Agonist	Main Findings
			tolerant individuals. The Mo-DC maturation was accompanied by the production of IFN-γ and IL-10 (Losada Mendez et al., 2021).
	TLR7/ TLR8	Imiquimode, Resiquimod (R848)	Transgenic mice carrying OVA-specific T cells receiving OVA-plasmid DNA vaccination by gene gun were subsequently subcutaneously injected with imiquimode or R848. Both imiquimode and R848 were able to establish a Th1-biased response as observed by the increase in the number of IFN-γ producing T cells compared to IL-4 producing $CD4^+$ T cells. The activity of R848 was 10-fold lower compared to imiquimode (Thomsen et al., 2004).
		Resiquimod (R848)	An experimental airway allergic disease mouse model was treated with nasal instillation of nanoparticles (Rexo) containing R848, antigen and MHC-II, or control exosomes. Rexo- treated mice induced Ag-specific Tregs that inhibit Ag-specific Th2 cells, accompanied by the attenuation of airway allergic disease symptoms, suggesting the potential use of R848 in the treatment of airway allergies (Ma et al., 2021).
	TLR8	VTX-1463	VTX-1463 pre-treatment in Ragweed (RW)-sensitized dogs prior to RW challenge significantly preserved the nasal cavity volume during the acute response, accompanied by the reduction in the levels of mast cell mediators such as histamine, PGE2, PGD2, and cysteinyl LTs when compared to the placebo treatment (Royer et al., 2016).
	TLR9	CYT003-QbG10 (CpG packaged in VLP)	HDM allergic patients treated with a high dose of CYT003-QbG10 **(allergen-independent treatment**) had lower rhinoconjunctivitis scores and reported a better QoL compared to the placebo-treated group. The allergen provocation test additionally demonstrated a 10-fold increase in allergen tolerance in the high-dose treatment group compared to placebo (Klimek et al., 2011). HDM allergic patients were given AIT of HDM extract admixed with CYT003-QbG10 via SCIT for 10 weeks in a Phase I/IIa clinical study. The AIT was well tolerated, and patients reported almost no allergic symptoms by the end of the therapy. The symptom-free period lasted 38 weeks beyond the AIT treatment. In addition, allergen skin reactivity was reduced, but patients had higher titres of allergen-specific IgG (Senti et al., 2009).
		QbG10	All asthmatic patients injected with QbG10 (**allergen-independent**) (n = 33) reported improvements in symptom and medication scores compared to the placebo-treated group (n = 30). By the end of the study, two-thirds of QbG10-treated patients reported well-controlled asthma. FEV1 values in the QbG10 group remained unchanged at the end of the study, but that of the placebo group significantly deteriorated (Beeh et al., 2013).

and reduced toxicity (Alberca-Custodio et al., 2020; Li and Mooney, 2016; Wang et al., 2018). Importantly, most experimental models, including mouse models and early human clinical trials, have utilized shorter treatment schedules for AIT, with comparable outcomes to traditional AIT. In some instances, the administration of TLR agonist alone, independent of allergen, has demonstrated clinical improvements of allergic conditions (Beeh et al., 2013; Klimek et al., 2011). Clinical trials have primarily focused on a limited range of TLR agonists, primarily those targeting TLR 4 and 9 (Kirtland et al., 2020). However, the confirmation of the beneficial use of various TLR agonist molecules as adjuvants in AIT awaits validation in larger-scale clinical trials.

4.3.3. *Virus-like particles*

Virus-like particles (VLPs) refer to self-assembling particles of a virus, encompassing capsid, core, and envelope proteins. Virus-like

particles are not infectious as they do not contain the viral genetic material, but are highly immunogenic and provide adjuvant properties when used in AIT preparations. Few VLP-based vaccines have been approved by the regulatory authorities such as against the human papillomavirus (Cheng et al., 2020) and hepatitis E virus (Cao et al., 2018). So far, no studies have been done on VLP-based cockroach AIT. Studies of other AIT preparations against inhalant and food allergens using VLPs have demonstrated that these molecules are well tolerated and able to protect against anaphylaxis reactions upon allergen re-stimulation (Schmitz et al., 2009; Storni et al., 2020; Zeltins et al., 2017).

4.3.4. Biologics

In a polysensitized patient with high total and specific IgE, AIT alone may be insufficient in improving clinical symptoms, due to the presence of free IgE. Monoclonal anti-IgE antibodies (such as Omalizumab) co-administered with AIT has been shown to decrease the levels of free IgE in the serum, which reduces the incidences of IgE-mediated adverse events (Kopp et al., 2013, 2009; Massanari et al., 2010). In particular, pre-treatment of patients with severe asthma with Omalizumab, allowed for these patients to be treated safely with AIT (Valdesoiro-Navarrete et al., 2022). A combination of Omalizumab and AIT was shown to be significantly affective in improving clinical outcomes and reduce medication use among house dust mite-driven asthmatics (Bozek et al., 2023).

Interleukin (IL)− 9 is produced by several immune cells, including Th2 cells, and promotes IgE production, mast cell proliferation, and epithelial chemokine and mucus production (Brough et al., 2014; Sehra et al., 2015). The effect of anti-IL-9 treatment in conjunction with AIT has been mixed. In a double-blind, multicenter, parallel-group study, patients with confirmed moderate-to-severe asthma were randomized to receive a placebo or anti-IL-9, in addition to their usual asthma medications. The addition of anti-IL-9 did not improve the clinical symptoms, asthma exacerbation, or FEV1 values in this study (Oh et al., 2013). However, the effect of anti-IL-9 treatment in conjunction with AIT in a mouse model of allergic rhinitis demonstrated a reduction in allergic symptoms, decreased specific IgE levels, and eosinophil infiltration. The treatment also increased IL-10 mRNA expression as well as the induction of $CD4^{+}CD25^{+}Foxp3^{+}$ T cells, suggesting an increase in tolerance induction (Shin et al., 2017).

Thymic stromal lymphopoietin (TSLP) is a cytokine that plays a key role in maintaining immune homeostasis and regulates the inflammatory responses at the mucosal barriers. A monoclonal antibody that specifically recognizes TSLP, Tezepelumab, is currently being tested in a clinical trial to evaluate if the combination of anti-TSLP with AIT is able to induce tolerance responses in individuals with cat allergy (clinicaltrials.gov, NCT02237196). Based on preliminary results, patients treated with anti-TSLP with cat AIT showed the lowest total nasal symptom scores, suggesting the potential use of this antibody in the treatment of asthma.

Severe asthmatic patients with the eosinophilic subtype may benefit from pre-treatment with anti-IL5 therapies to control their asthma. A case study involving a 67-year-old male patient with this specific subtype of asthma demonstrated successful outcomes in AIT after his severe asthmatic symptoms improved with the use of Mepolizumab, an anti-IL5 antibody. This treatment approach proved effective after the patient did not respond to Omalizumab (Gulsen et al., 2021).

While the addition of biologics to AIT has shown promising results, larger clinical trials are required to determine the optimal treatment dose and duration of therapy based on the allergic phenotype and the sensitization profiles of the patients.

4.4. Delivery systems

In many cases, nanostructures that are used as a ‘vehicle’ to deliver AIT to the target cells play additional roles of having depot effects and able to stimulate the immune system due to adjuvant properties. Nanostructures can also be used to target the therapeutic agent directly to immune cells. In the case of AIT, it is conceivable for the AIT preparation to be targeted to dendritic cells (DCs), as they play a central role in allergen processing and presentation to T cells. This can be achieved by targeting the DNA vaccines to DCs via mannose receptors, which have been experimented with in melanoma immunotherapy (Moku et al., 2021).

Another novel strategy is using genetically engineered dendritic cells as immunotherapy (Kim et al., 2021). The antigen-processing molecules VPS37A and VPS37B on DCs have been identified as potential therapeutic targets to treat allergic rhinitis. A genetically engineered myeloid DC with disrupted VPS37A/B using the CRISPR/Cas9 system showed significant reductions in Th2 cytokine production and reduced allergic responses in an allergic rhinitis mice model (Kim et al., 2021). The application of other nanostructures in allergen immunotherapy has been recently reviewed (Mayorga et al., 2021). Harnessing the right nanostructure based on their physical and chemical properties will allow for better targeting of AIT molecules to improve uptake, and reduce undesired adverse effects.

Liposomes possess a unique capability to encapsulate allergens for immunotherapy delivery, acting as a protective layer against allergen degradation, and facilitating precise targeting of the allergen to antigen-presenting cells. Liposomes are usually made up of naturally occurring lipids and hence are non-toxic and biodegradable. Liposomes have been efficacious in the delivery of AIT subcutaneously (Basomba et al., 2002), sublingually (Aliu et al., 2017) and intranasally (Chaisri et al., 2017; Meechan et al., 2013) demonstrating adjuvant properties that improve the tolerance mechanism.

Gold nanoparticles have been used as drug carriers, with a good safety profile. More recently, they have been employed as a delivery system in AIT. A research group from Iran demonstrated, using mouse models, the effectiveness of aptamer-modified gold nanoparticles containing allergen in improving Th1 and Treg immuno-modulatory responses (Koushki et al., 2020; Sadeghi et al., 2020). Larger trials are needed to assess the translatability of these positive results in real-life scenarios.

Poly (lactic-co-glycolic acid) or PGLA has been researched as a carrier for allergen immunotherapy for over 15 years. The structure of PGLA used may be customized by modification of surface charge, hydrophobicity, shape, and charge that makes it an attractive carrier to suit different allergens. PGLA-coupled allergen immunotherapy preparations have shown positive results even with reduced AIT preparation doses (Salari et al., 2015) and different immunization routes (Keshavarz Shahbaz et al., 2020).

Apart from delivery systems, routes of delivery could also impact the immune outcomes of immunotherapy. Allergen immunotherapy can be administered via several routes, but at present, subcutaneous (SCIT) and sublingual (SLIT) is the most common. Subcutaneous immunotherapy involves the administration of weekly incremental doses of the AIT preparation via injections for 3–6 months until a maintenance dose is achieved, and, monthly injections with a high dose of the AIT preparation for 3–5 years. All SCIT doses must be administered in a clinic. Sublingual immunotherapy involves the administration of high-dose AIT preparation under the tongue either in the form of a dissolving tablet or as a solution for a period of 3 years. Apart from the first SLIT administration in the clinic, the remaining doses can be taken in the patient’s home. In a recent meta-analysis, no significant differences were identified between SCIT and SLIT in terms of treatment efficacy, improvement of clinical symptoms, and reduction in medication use. However, SCIT tended to have more systemic adverse reactions and anaphylaxis compared to SLIT administrations (Field and Blaiss, 2020). Newer routes of AIT delivery are being tested to address the current limitations in AIT – namely reducing any adverse effects, and shortening the time of the therapy.

Intralymphatic immunotherapy (ILIT) exhibits promising efficacy,

utilizing lower allergen concentrations and shorter treatment durations compared to SCIT. Currently, the ILIT approach has been investigated for grass and tree pollens as well as cat dander. The primary challenges associated with this method include the necessity for ultrasound equipment to guide the intralymphatic injections and patient hesitation towards injection at that particular site (Senti et al., 2019). EPIT, which delivers AIT via skin patches, offers a non-invasive treatment option. It has been tested for both respiratory and food allergens, showing promising outcomes (Bird et al., 2018). However, despite its positive immunotherapy outcomes, patient compliance and accurate dosing remain challenges that require further attention (Aricigil et al., 2016).

5. The future outlook for cockroach AIT

Cockroaches are an important allergen source that can be found ubiquitously. Environmental exposure to cockroach allergens has been identified as an important risk factor in cockroach allergen sensitization and the subsequent development of respiratory allergic diseases. Due to the challenging nature of eliminating cockroach allergens from indoor environments, immunotherapy emerges as an appealing long-term treatment solution.

However, in its present form, AIT has some limitations that need to be addressed. First, the use of extracts that are prone to content and quality variability should be replaced by defined allergens that now can be produced easily in the laboratory. This will provide reproducible and standardized therapeutic molecules that are free from toxins and other contaminating material. Second, the use of whole allergens as found in the extracts also frequently results in undesired allergic reactions. Allergen modification by removing the IgE epitopes but retaining other immune structures of the allergen, either by genetically engineering the allergen or synthetic T- or B- cell epitopes could provide similar immunomodulatory outcomes without the undesired adverse effects. An additional consideration, especially for allergen sources lacking a dominant allergen, such as cockroach allergens, is to focus on immunotherapy based on allergen groups (eg tropomyosin, arginine kinase, etc), rather than the specific allergen source. This approach is supported by numerous reports highlighting cross-reactivity among allergen groups.

Third, the duration of the ‘standard’ three-year immunotherapy has been a subject of debate due to its associated time and cost burden. However, research focusing on newer adjuvants, delivery methods, and routes has shown promising results in reducing the duration of immunotherapy and minimizing the occurrence of adverse events associated with AIT. Additionally, exploring other aspects of immunotherapy such as the incorporation of micronutrients like vitamin D (Heine et al., 2021) or probiotics (Nabil et al., 2020) as supplementary treatments, holds the potential to enhance efficacy and further decrease treatment duration.

The success of an immunotherapy protocol is also largely dependent on accurate patient selection. The integration of precision allergen testing through component-resolved diagnosis would be essential in matching the right patients with the appropriate allergens for immunotherapy. Ensuring accurate patient diagnosis and treatment would facilitate more targeted interventions, leading to enhanced clinical outcomes and improved quality of life for individuals with allergies.

Declaration of Competing Interest

KR declare no competing interests. FTC has received consultancy fees from Sime Darby Technology Centre, First Resources Ltd, Genting Plantation, Olam International, and Syngenta Crop Protection, outside the submitted work.

Data availability

No data was used for the research described in the article.

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References

Akdis, M., Akdis, C.A., 2007. Mechanisms of allergen-specific immunotherapy. J. Allergy Clin. Immunol. 119, 780–791.

Akinfenwa, O., Rodriguez-Dominguez, A., Vrtala, S., Valenta, R., Campana, R., 2021. Novel vaccines for allergen-specific immunotherapy. Curr. Opin. Allergy Clin. Immunol. 21, 86–99.

Alberca-Custodio, R.W., Faustino, L.D., Gomes, E., Nunes, F.P.B., de Siqueira, M.K., Labrada, A., Almeida, R.R., Camara, N.O.S., da Fonseca, D.M., Russo, M., 2020. Allergen-specific immunotherapy with liposome containing CpG-ODN in murine model of asthma relies on MyD88 signaling in dendritic cells. Front. Immunol. 11, 692.

Aliu, H., Rask, C., Brimnes, J., Andresen, T.L., 2017. Enhanced efficacy of sublingual immunotherapy by liposome-mediated delivery of allergen. Int. J. Nanomed. 12, 8377–8388.

Aricigil, M., Muluk, N.B., Sakarya, E.U., Sakalar, E.G., Senturk, M., Reisacher, W.R., Cingi, C., 2016. New routes of allergen immunotherapy. Am. J. Rhinol. Allergy 30, 193–197.

Arruda, L.K., Vailes, L.D., Mann, B.J., Shannon, J., Fox, J.W., Vedvick, T.S., Hayden, M. L., Chapman, M.D., 1995. Molecular cloning of a major cockroach (Blattella germanica) allergen, Bla g 2. Sequence homology to the aspartic proteases. J. Biol. Chem. 270, 19563–19568.

Baker Jr., J.R., Rasky, A.J., Landers, J.J., Janczak, K.W., Totten, T.D., Lukacs, N.W., O'Konek, J.J., 2021. Intranasal delivery of allergen in a nanoemulsion adjuvant inhibits allergen-specific reactions in mouse models of allergic airway disease. Clin. Exp. Allergy 51, 1361–1373.

Basomba, A., Tabar, A.I., de Rojas, D.H., Garcia, B.E., Alamar, R., Olaguibel, J.M., del Prado, J.M., Martin, S., Rico, P., 2002. Allergen vaccination with a liposome-encapsulated extract of Dermatophagoides pteronyssinus: a randomized, double-blind, placebo-controlled trial in asthmatic patients. J. Allergy Clin. Immunol. 109, 943–948.

Beeh, K.M., Kanniess, F., Wagner, F., Schilder, C., Naudts, I., Hammann-Haenni, A., Willers, J., Stocker, H., Mueller, P., Bachmann, M.F., Renner, W.A., 2013. The novel TLR-9 agonist QbG10 shows clinical efficacy in persistent allergic asthma. J. Allergy Clin. Immunol. 131, 866–874.

Bird, J.A., Sanchez-Borges, M., Ansotegui, I.J., Ebisawa, M., Ortega Martell, J.A., 2018. Skin as an immune organ and clinical applications of skin-based immunotherapy. World Allergy Organ. J. 11, 38.

Birrueta, G., Frazier, A., Pomes, A., Glesner, J., Filep, S., Schal, C., Jeong, K.Y., McMurtrey, C., Vander Schans, T., Hildebrand, W.H., Busse, P., Beigelman, A., Bacharier, L.B., Peters, B., Sette, A., Schulten, V., 2019. Variability in German cockroach extract composition greatly impacts T cell potency in cockroach-allergic donors. Front. Immunol. 10, 313.

Bousquet, J., Anto, J.M., Wickman, M., Keil, T., Valenta, R., Haahtela, T., Lodrup Carlsen, K., van Hage, M., Akdis, C., Bachert, C., Akdis, M., Auffray, C., Annesi-Maesano, I., Bindslev-Jensen, C., Cambon-Thomsen, A., Carlsen, K.H., Chatzi, L., Forastiere, F., Garcia-Aymerich, J., Gehrig, U., Guerra, S., Heinrich, J., Koppelman, G.H., Kowalski, M.L., Lambrecht, B., Lupinek, C., Maier, D., Melen, E., Momas, I., Palkonen, S., Pinart, M., Postma, D., Siroux, V., Smit, H.A., Sunyer, J., Wright, J., Zuberbier, T., Arshad, S.H., Nadif, R., Thijs, C., Andersson, N., Asarnoj, A., Ballardini, N., Ballereau, S., Bedbrook, A., Benet, M., Bergstrom, A., Brunekreef, B., Burte, E., Calderon, M., De Carlo, G., Demoly, P., Eller, E., Fantini, M. P., Hammad, H., Hohman, C., Just, J., Kerkhof, M., Kogevinas, M., Kull, I., Lau, S., Lemonnier, N., Mommers, M., Nawijn, M., Neubauer, A., Oddie, S., Pellet, J., Pin, I., Porta, D., Saes, Y., Skrindo, I., Tischer, C.G., Torrent, M., von Hertzen, L., 2015. Are

allergic multimorbidities and IgE polysensitization associated with the persistence or re-occurrence of foetal type 2 signalling? The MeDALL hypothesis. Allergy 70, 1062–1078.

Bousquet, J., Pfaar, O., Agache, I., Bedbrook, A., Akdis, C.A., Canonica, G.W., Chivato, T., Al-Ahmad, M., Abdul Latiff, A.H., Ansotegui, I.J., Bachert, C., Baharuddin, A., Bergmann, K.C., Bindslev-Jensen, C., Bjermer, L., Bonini, M., Bosnic-Anticevich, S., Bosse, I., Brough, H.A., Brussino, L., Calderon, M.A., Caraballo, L., Cardona, V., Carreiro-Martins, P., Casale, T., Cecchi, L., Cepeda Sarabia, A.M., Chkhartishvili, E., Chu, D.K., Cirule, I., Cruz, A.A., Czarlewski, W., Del Giacco, S., Demoly, P., Devillier, P., Dokic, D., Durham, S.L., Ebisawa, M., El-Gamal, Y., Emuzyte, R., Gamkrelidze, A., Fauquert, J.L., Fiocchi, A., Fokkens, W.J., Fonseca, J.A., Fontaine, J.F., Gawlik, R., Gelincik, A., Gemicioglu, B., Gereda, J.E., Gerth van Wijk, R., Gomez, R.M., Gotua, M., Grisle, I., Guzman, M.A., Haahtela, T., Halken, S., Heffler, E., Hoffmann-Sommergruber, K., Hossny, E., Hrubisko, M., Irani, C., Ivancevich, J.C., Ispayeva, Z., Julge, K., Kaidashev, I., Kalayci, O., Khaitov, M., Klimek, L., Knol, E., Kowalski, M.L., Kraxner, H., Kull, I., Kuna, P., Kvedariene, V., Kritikos, V., Lauerma, A., Lau, S., Laune, D., Levin, M., Larenas-Linnemann, D.E., Lodrup Carlsen, K.C., Lombardi, C., Lourenco, O.M., Mahboub, B., Malling, H.J., Manning, P., Marshall, G.D., Melen, E., Meltzer, E.O., Miculinic, N., Milenkovic, B., Moin, M., Montefort, S., Morais-Almeida, M., Mortz, C.G., Mosges, R., Mullol, J., Namazova Baranova, L., Neffen, H., Nekam, K., Niedoszytko, M., Odemyr, M., O'Hehir, R.E., Ollert, M., O'Mahony, L., Ohta, K., Okamoto, Y., Okubo, K., Pajno, G. B., Palomares, O., Palkonen, S., Panzner, P., N, G.P., Park, H.S., Passalacqua, G., Patella, V., Pawankar, R., Pham-Thi, N., Plavec, D., Popov, T.A., Recto, M., Regateiro, F.S., Riggioni, C., Roberts, G., Rodriguez-Gonzales, M., Rosario, N., Rottem, M., Rouadi, P.W., Ryan, D., Samolinski, B., Sanchez-Borges, M., Serpa, F.S., Sastre, J., Scadding, G.K., Shamji, M.H., Schmid-Grendelmeier, P., Schunemann, H. J., Sheikh, A., Scichilone, N., Sisul, J.C., Sofiev, M., Sole, D., Sooronbaev, T., Soto-Martinez, M., Soto-Quiros, M., Sova, M., Schwarze, J., Skypala, I., Suppli-Ulrik, C., Taborda-Barata, L., Todo-Bom, A., Torres, M.J., Valentin-Rostan, M., Tomazic, P.V., Valero, A., Toppila-Salmi, S., Tsiligianni, I., Untersmayr, E., Urrutia-Pereira, M., Valiulis, A., Valovirta, E., Vandenplas, O., Ventura, M.T., Vichyanond, P., Wagenmann, M., Wallace, D., Walusiak-Skorupa, J., Wang, Y., Waserman, S., Wong, G.W., Yorgancioglu, A., Yusuf, O.M., Zernotti, M., Zhang, L., Zidarn, M., Zuberbier, T., Jutel, M., 2021. ARIA-EAACI care pathways for allergen immunotherapy in respiratory allergy. Clin. Transl. Allergy 11, e12014.

Bousquet, J., Schunemann, H.J., Togias, A., Bachert, C., Erhola, M., Hellings, P.W., Klimek, L., Pfaar, O., Wallace, D., Ansotegui, I., Agache, I., Bedbrook, A., Bergmann, K.C., Bewick, M., Bonniaud, P., Bosnic-Anticevich, S., Bosse, I., Bouchard, J., Boulet, L.P., Brozek, J., Brusselle, G., Calderon, M.A., Canonica, W.G., Caraballo, L., Cardona, V., Casale, T., Cecchi, L., Chu, D.K., Costa, E.M., Cruz, A.A., Czarlewski, W., D'Amato, G., Devillier, P., Dykewicz, M., Ebisawa, M., Fauquert, J. L., Fokkens, W.J., Fonseca, J.A., Fontaine, J.F., Gemicioglu, B., van Wijk, R.G., Haahtela, T., Halken, S., Ierodiakonou, D., Iinuma, T., Ivancevich, J.C., Jutel, M., Kaidashev, I., Khaitov, M., Kalayci, O., Kleine Tebbe, J., Kowalski, M.L., Kuna, P., Kvedariene, V., La Grutta, S., Larenas-Linnemann, D., Lau, S., Laune, D., Le, L., Lieberman, P., Lodrup Carlsen, K.C., Lourenco, O., Marien, G., Carreiro-Martins, P., Melen, E., Menditto, E., Neffen, H., Mercier, G., Mosgues, R., Mullol, J., Muraro, A., Namazova, L., Novellino, E., O'Hehir, R., Okamoto, Y., Ohta, K., Park, H.S., Panzner, P., Passalacqua, G., Pham-Thi, N., Price, D., Roberts, G., Roche, N., Rolland, C., Rosario, N., Ryan, D., Samolinski, B., Sanchez-Borges, M., Scadding, G. K., Shamji, M.H., Sheikh, A., Bom, A.T., Toppila-Salmi, S., Tsiligianni, I., Valentin-Rostan, M., Valiulis, A., Valovirta, E., Ventura, M.T., Walker, S., Waserman, S., Yorgancioglu, A., Zuberbier, T., Allergic, R., Its Impact on Asthma Working, G., 2020. Next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for allergic rhinitis based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and real-world evidence. J. Allergy Clin. Immunol. 145, 70–80 e73.

Bozek, A., Fischer, A., Bogacz-Piaseczynska, A., Canonica, G.W., 2023. Adding a biologic to allergen immunotherapy increases treatment efficacy. ERJ Open Res. 9.

Brenner, B.L., Markowitz, S., Rivera, M., Romero, H., Weeks, M., Sanchez, E., Deych, E., Garg, A., Godbold, J., Wolff, M.S., Landrigan, P.J., Berkowitz, G., 2003. Integrated pest management in an urban community: a successful partnership for prevention. Environ. Health Perspect. 111, 1649–1653.

Brough, H.A., Cousins, D.J., Munteanu, A., Wong, Y.F., Sudra, A., Makinson, K., Stephens, A.C., Arno, M., Ciortuz, L., Lack, G., Turcanu, V., 2014. IL-9 is a key component of memory TH cell peanut-specific responses from children with peanut allergy. J. Allergy Clin. Immunol. 134 (1329–1338), e1310.

Cao, Y., Bing, Z., Guan, S., Zhang, Z., Wang, X., 2018. Development of new hepatitis E vaccines. Hum. Vaccin. Immunother. 14, 2254–2262.

Chaisri, U., Tungtrongchitr, A., Indrawattana, N., Meechan, P., Phurttikul, W., Tasaniyananda, N., Saelim, N., Chaicumpa, W., Sookrung, N., 2017. Immunotherapeutic efficacy of liposome-encapsulated refined allergen vaccines against Dermatophagoides pteronyssinus allergy. PLoS One 12, e0188627.

Chen, K.W., Zieglmayer, P., Zieglmayer, R., Lemell, P., Horak, F., Bunu, C.P., Valenta, R., Vrtala, S., 2019. Selection of house dust mite-allergic patients by molecular diagnosis may enhance success of specific immunotherapy. J. Allergy Clin. Immunol. 143, 1248–1252 e1212.

Cheng, L., Wang, Y., Du, J., 2020. Human papillomavirus vaccines: an updated review. Vaccines, 8.

Dzoro, S., Mittermann, I., Resch-Marat, Y., Vrtala, S., Nehr, M., Hirschl, A.M., Wikberg, G., Lundeberg, L., Johansson, C., Scheynius, A., Valenta, R., 2018. House dust mites as potential carriers for IgE sensitization to bacterial antigens. Allergy 73, 115–124.

Englert, L., Mahler, V., Bonertz, A., 2021. Regulatory requirements for the quality of allergen products for allergen immunotherapy of food allergy. Curr. Allergy Asthma Rep. 21, 32-32.

Field, K., Blaiss, M.S., 2020. Sublingual versus subcutaneous immunotherapy for allergic rhinitis: what are the important therapeutic and real-world considerations? Curr. Allergy Asthma Rep. 20, 45.

Florido-Lopez, J.F., Andreu-Balaguer, C., Escudero, C., Seoane-Rodriguez, M., Hernandez, M., Navarro-Seisdedos, L.A., Torrecillas-Toro, M., Anton-Girones, M., Herrero-Lifona, L., Brugaletta, D., Macias, J., Pineda, R., Lara, M.A., Lopez-Caballero, J., Rojas, M.J., 2020. Effectiveness and safety of a glutaraldehyde-modified, L-tyrosine-adsorbed and monophosphoryl lipid A-Adjuvanted allergen immunotherapy in patients with allergic asthma sensitized to olive pollen: a retrospective, controlled real-world study. World Allergy Organ. J. 13, 100487.

Focke-Tejkl, M., Weber, M., Niespodziana, K., Neubauer, A., Huber, H., Henning, R., Stegfellner, G., Maderegger, B., Hauer, M., Stolz, F., Niederberger, V., Marth, K., Eckl-Dorna, J., Weiss, R., Thalhamer, J., Blatt, K., Valent, P., Valenta, R., 2015. Development and characterization of a recombinant, hypoallergenic, peptide-based vaccine for grass pollen allergy. J. Allergy Clin. Immunol. 135, 1207-1207 e1201-1211.

Fuchs, B., Knothe, S., Rochlitzer, S., Nassimi, M., Greweling, M., Lauenstein, H.D., Nassenstein, C., Muller, M., Ebensen, T., Dittrich, A.M., Krug, N., Guzman, C.A., Braun, A., 2010. A Toll-like receptor 2/6 agonist reduces allergic airway inflammation in chronic respiratory sensitisation to Timothy grass pollen antigens. Int. Arch. Allergy Immunol. 152, 131–139.

Fukutomi, Y., Kawakami, Y., 2021. Respiratory sensitization to insect allergens: species, components and clinical symptoms. Allergol. Int. 70, 303–312.

Gerhold, K., Avagyan, A., Reichert, E., Blumchen, K., Wahn, U., Hamelmann, E., 2008. Lipopolysaccharides modulate allergen-specific immune regulation in a murine model of mucosal tolerance induction. Int. Arch. Allergy Immunol. 147, 25–34.

Glesner, J., Filep, S., Vailes, L.D., Wunschmann, S., Chapman, M.D., Birrueta, G., Frazier, A., Jeong, K.Y., Schal, C., Bacharier, L., Beigelman, A., Busse, P., Schulten, V., Sette, A., Pomes, A., 2019. Allergen content in German cockroach extracts and sensitization profiles to a new expanded set of cockroach allergens determine in vitro extract potency for IgE reactivity. J. Allergy Clin. Immunol. 143 (1474–1481), e1478.

Gold, D.R., Burge, H.A., Carey, V., Milton, D.K., Platts-Mills, T., Weiss, S.T., 1999. Predictors of repeated wheeze in the first year of life: the relative roles of cockroach, birth weight, acute lower respiratory illness, and maternal smoking. Am. J. Respir. Crit. Care Med. 160, 227–236.

Gulsen, A., Wallis, S., Jappe, U., 2021. Combination of immunotherapies for severe allergic asthma. J. Asthma 58, 75–78.

Heine, S., Aguilar-Pimentel, A., Russkamp, D., Alessandrini, F., Gailus-Durner, V., Fuchs, H., Ollert, M., Bredehorst, R., Ohnmacht, C., Zissler, U.M., Hrabe de Angelis, M., Schmidt-Weber, C.B., Blank, S., 2022. Thermosensitive PLGA-PEG-PLGA hydrogel as depot matrix for allergen-specific immunotherapy. Pharmaceutics 14.

Heine, G., Francuzik, W., Doelle-Bierke, S., Drozdenko, G., Frischbutter, S., Schumacher, N., Radbruch, A., Worm, M., 2021. Immunomodulation of high-dose vitamin D supplementation during allergen-specific immunotherapy. Allergy 76, 930–933.

Hossenbaccus, L., Linton, S., Garvey, S., Ellis, A.K., 2020. Towards definitive management of allergic rhinitis: best use of new and established therapies. Allergy Asthma Clin. Immunol. 16, 39.

Huang, H.J., Curin, M., Banerjee, S., Chen, K.W., Garmatiuk, T., Resch-Marat, Y., Carvalho-Queiroz, C., Blatt, K., Gafvelin, G., Gronlund, H., Valent, P., Campana, R., Focke-Tejkl, M., Valenta, R., Vrtala, S., 2019. A hypoallergenic peptide mix containing T cell epitopes of the clinically relevant house dust mite allergens. Allergy 74, 2461–2478.

Investigators, P.Go.C., Vickery, B.P., Vereda, A., Casale, T.B., Beyer, K., du Toit, G., Hourihane, J.O., Jones, S.M., Shreffler, W.G., Marcantonio, A., Zawadzki, R., Sher, L., Carr, W.W., Fineman, S., Greos, L., Rachid, R., Ibanez, M.D., Tilles, S., Assa'ad, A.H., Nilsson, C., Rupp, N., Welch, M.J., Sussman, G., Chinthrajah, S., Blumchen, K., Sher, E., Spergel, J.M., Leickly, F.E., Zielen, S., Wang, J., Sanders, G. M., Wood, R.A., Cheema, A., Bindslev-Jensen, C., Leonard, S., Kachru, R., Johnston, D.T., Hampel, F.C., Jr, Kim, Anagnostou, E.H., Pongracic, A., Ben-Shoshan, J.A., Sharma, M., Stillerman, H.P., Windom, A., Yang, H.H., Muraro, W.H., Zubeldia, A., Sharma, J.M., Dorsey, V., Chong, M.J., Ohayon, H.J., Bird, J., Carr, J. A., Siri, T.F., Fernandez-Rivas, D., Jeong, M., Fleischer, D.K., Lieberman, D.M., Dubois, J.A., Tsoumani, A.E.J., Ciaccio, M., Portnoy, C.E., Mansfield, J.M., Fritz, L. E., Lanser, S.B., Matz, B.J., Oude Elberink, J., Varshney, H.N.G., Dilly, P., Adelman, S.G., Burks, A.W, D.C., 2018. AR101 oral immunotherapy for peanut allergy. N. Engl. J. Med. 379, 1991–2001.

Jensen-Jarolim, E., 2015. Aluminium in allergies and allergen immunotherapy. World Allergy Organ. J. 8, 7.

Jutel, M., Bruggenjurgen, B., Richter, H., Vogelberg, C., 2020. Real-world evidence of subcutaneous allergoid immunotherapy in house dust mite-induced allergic rhinitis and asthma. Allergy 75, 2050–2058.

Kang, B.C., Johnson, J., Morgan, C., Chang, J.L., 1988. The role of immunotherapy in cockroach asthma. J. Asthma 25, 205–218.

Keshavarz Shahbaz, S., Varasteh, A.R., Koushki, K., Ayati, S.H., Mashayekhi, K., Sadeghi, M., Moghadam, M., Sankian, M., 2020. Sublingual dendritic cells targeting by aptamer: Possible approach for improvement of sublingual immunotherapy efficacy. Int. Immunopharmacol. 85, 106603.

Kim, B., Lee, Y.E., Yeon, J.W., Go, G.Y., Byun, J., Lee, K., Lee, H.K., Hur, J.K., Jang, M., Kim, T.H., 2021. A novel therapeutic modality using CRISPR-engineered dendritic cells to treat allergies. Biomaterials 273, 120798.

Kinney, P.L., Northridge, M.E., Chew, G.L., Gronning, E., Joseph, E., Correa, J.C., Prakash, S., Goldstein, I., 2002. On the front lines: an environmental asthma intervention in New York City. Am. J. Public Health 92, 24–26.
Kirtland, M.E., Tsitoura, D.C., Durham, S.R., Shamji, M.H., 2020. Toll-like receptor agonists as adjuvants for allergen immunotherapy. Front. Immunol. 11, 599083.
Kitzmuller, C., Kalser, J., Mutschlechner, S., Hauser, M., Zlabinger, G.J., Ferreira, F., Bohle, B., 2018. Fusion proteins of flagellin and the major birch pollen allergen Bet v 1 show enhanced immunogenicity, reduced allergenicity, and intrinsic adjuvanticity. J. Allergy Clin. Immunol. 141 (293–299), e296.
Klimek, L., Bachert, C., Lukat, K.F., Pfaar, O., Meyer, H., Narkus, A., 2015. Allergy immunotherapy with a hypoallergenic recombinant birch pollen allergen rBet v 1-FV in a randomized controlled trial. Clin. Transl. Allergy 5, 28.
Klimek, L., Willers, J., Hammann-Haenni, A., Pfaar, O., Stocker, H., Mueller, P., Renner, W.A., Bachmann, M.F., 2011. Assessment of clinical efficacy of CYT003-QbG10 in patients with allergic rhinoconjunctivitis: a phase IIb study. Clin. Exp. Allergy 41, 1305–1312.
Kopp, M.V., Hamelmann, E., Bendiks, M., Zielen, S., Kamin, W., Bergmann, K.C., Klein, C., Wahn, U., group, Ds, 2013. Transient impact of omalizumab in pollen allergic patients undergoing specific immunotherapy. Pediatr. Allergy Immunol. 24, 427–433.
Kopp, M.V., Hamelmann, E., Zielen, S., Kamin, W., Bergmann, K.C., Sieder, C., Stenglein, S., Seyfried, S., Wahn, U., group, Ds, 2009. Combination of omalizumab and specific immunotherapy is superior to immunotherapy in patients with seasonal allergic rhinoconjunctivitis and co-morbid seasonal allergic asthma. Clin. Exp. Allergy 39, 271–279.
Koushki, K., Varasteh, A.R., Shahbaz, S.K., Sadeghi, M., Mashayekhi, K., Ayati, S.H., Moghadam, M., Sankian, M., 2020. Dc-specific aptamer decorated gold nanoparticles: A new attractive insight into the nanocarriers for allergy epicutaneous immunotherapy. Int. J. Pharm. 584, 119403.
Larche, M., 2011. T cell epitope-based allergy vaccines. Curr. Top. Microbiol. Immunol. 352, 107–119.
Lee, M.F., Chang, C.W., Song, P.P., Hwang, G.Y., Lin, S.J., Chen, Y.H., 2015. IgE-binding epitope mapping and tissue localization of the major American Cockroach Allergen Per a 2. Allergy Asthma Immunol. Res. 7, 376–383.
Leuthard, D.S., Duda, A., Freiberger, S.N., Weiss, S., Dommann, I., Fenini, G., Contassot, E., Kramer, M.F., Skinner, M.A., Kundig, T.M., Heath, M.D., Johansen, P., 2018. Microcrystalline tyrosine and aluminum as adjuvants in allergen-specific immunotherapy protect from ige-mediated reactivity in mouse models and act independently of inflammasome and TLR signaling. J. Immunol. 200, 3151–3159.
Li, J., Mooney, D.J., 2016. Designing hydrogels for controlled drug delivery. Nat. Rev. Mater. 1.
Liu, A.H., Babineau, D.C., Krouse, R.Z., Zoratti, E.M., Pongracic, J.A., O'Connor, G.T., Wood, R.A., Khurana Hershey, G.K., Kercsmar, C.M., Gruchalla, R.S., Kattan, M., Teach, S.J., Makhija, M., Pillai, D., Lamm, C.I., Gern, J.E., Sigelman, S.M., Gergen, P. J., Togias, A., Visness, C.M., Busse, W.W., 2016. Pathways through which asthma risk factors contribute to asthma severity in inner-city children. J. Allergy Clin. Immunol. 138, 1042–1050.
Losada Mendez, J., Palomares, F., Gomez, F., Ramirez-Lopez, P., Ramos-Soriano, J., Torres, M.J., Mayorga, C., Rojo, J., 2021. Immunomodulatory response of toll-like receptor ligand-peptide conjugates in food allergy. ACS Chem. Biol. 16, 2651–2664.
Lundberg, K., Rydnert, F., Broos, S., Andersson, M., Greiff, L., Lindstedt, M., 2016. Allergen-specific immunotherapy alters the frequency, as well as the FcR and CLR expression profiles of human dendritic cell subsets. PLoS One 11, e0148838.
Lupinek, C., Wollmann, E., Baar, A., Banerjee, S., Breiteneder, H., Broecker, B.M., Bublin, M., Curin, M., Flicker, S., Garmatiuk, T., Hochwallner, H., Mittermann, I., Pahr, S., Resch, Y., Roux, K.H., Srinivasan, B., Stentzel, S., Vrtala, S., Willison, L.N., Wickman, M., Lodrup-Carlsen, K.C., Anto, J.M., Bousquet, J., Bachert, C., Ebner, D., Schlederer, T., Harwanegg, C., Valenta, R., 2014. Advances in allergen-microarray technology for diagnosis and monitoring of allergy: the MeDALL allergen-chip. Methods 66, 106–119.
Ma, F., Zhang, Y.Y., Yang, G., Mo, L.H., Liu, D.B., Yang, L.T., Liu, Z.G., Ning, Y., Yang, P. C., 2021. Integrin alphavbeta6 cooperates with resiquimod to restore antigen-specific immune tolerance in airway allergy. Immunol. Lett. 230, 49–58.
Marrack, P., McKee, A.S., Munks, M.W., 2009. Towards an understanding of the adjuvant action of aluminium. Nat. Rev. Immunol. 9, 287–293.
Massanari, M., Nelson, H., Casale, T., Busse, W., Kianifard, F., Geba, G.P., Zeldin, R.K., 2010. Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma. J. Allergy Clin. Immunol. 125, 383–389.
Matsumoto, K., Kouzaki, H., Yamamoto, S., Kikuoka, H., Tojima, I., Ter Meulen, J.H., Shimizu, T., 2020. In vitro and in vivo inhibitory effects of TLR4 agonist, glucopyranosyl lipid A (GLA), on allergic rhinitis caused by Japanese cedar pollen. Allergy 75, 446–449.
Mayorga, C., Perez-Inestrosa, E., Rojo, J., Ferrer, M., Montanez, M.I., 2021. Role of nanostructures in allergy: diagnostics, treatments and safety. Allergy 76, 3292–3306.
Meechan, P., Tungtrongchitr, A., Chaisri, U., Maklon, K., Indrawattana, N., Chaicumpa, W., Sookrung, N., 2013. Intranasal, liposome-adjuvanted cockroach allergy vaccines made of refined major allergen and whole-body extract of Periplaneta americana. Int. Arch. Allergy Immunol. 161, 351–362.
Metenou, S., Nutman, T.B., 2013. Regulatory T cell subsets in filarial infection and their function. Front. Immunol. 4, 305.
Mohapatra, S.S., Qazi, M., Hellermann, G., 2010. Immunotherapy for allergies and asthma: present and future. Curr. Opin. Pharmacol. 10, 276–288.
Moingeon, P., Floch, V.B., Airouche, S., Baron-Bodo, V., Nony, E., Mascarell, L., 2016. Allergen immunotherapy for birch pollen-allergic patients: recent advances. Immunotherapy 8, 555–567.
Moku, G., Vangala, S., Gulla, S.K., Yakati, V., 2021. In vivo targeting of DNA vaccines to dendritic cells via the mannose receptor induces long-lasting immunity against melanoma. ChemBioChem 22, 523–531.
Moldaver, D.M., Bharhani, M.S., Rudulier, C.D., Wattie, J., Inman, M.D., Larche, M., 2019. Induction of bystander tolerance and immune deviation after Fel d 1 peptide immunotherapy. J. Allergy Clin. Immunol. 143 (1087–1099), e1084.
Moldaver, D., Larche, M., 2011. Immunotherapy with peptides. Allergy 66, 784–791.
Nabil, F., Elbehedy, E.M., Sedeek, R., Gouda, M.I., El Shahaway, A.A., 2020. Clinical efficacy of combined probiotics and immunotherapy in childhood allergic rhinitis. Egypt. J. Immunol. 27, 73–79.
Nalyanya, G., Gore, J.C., Linker, H.M., Schal, C., 2009. German cockroach allergen levels in North Carolina schools: comparison of integrated pest management and conventional cockroach control. J. Med. Entomol. 46, 420–427.
Oh, C.K., Leigh, R., McLaurin, K.K., Kim, K., Hultquist, M., Molfino, N.A., 2013. A randomized, controlled trial to evaluate the effect of an anti-interleukin-9 monoclonal antibody in adults with uncontrolled asthma. Respir. Res. 14, 93.
Padro, C., Gutierrez, D., Moreno, F., Parra, A., Rial, M.J., Lleonart, R., Toran-Barona, C., Justicia, J.L., Roger, A., 2022. Effectiveness and safety of a microcrystalline tyrosine-adjuvanted Dermatophagoides pteronyssinus allergoid immunotherapy in adult patients with allergic asthma and rhinitis: a real-life prospective observational study. Immun. Inflamm. Dis. 10, e585.
Patel, P., Holdich, T., Fischer von Weikersthal-Drachenberg, K.J., Huber, B., 2014. Efficacy of a short course of specific immunotherapy in patients with allergic rhinoconjunctivitis to ragweed pollen. J. Allergy Clin. Immunol. 133, 121-129 e121-122.
Pomes, A., Schulten, V., Glesner, J., da Silva Antunes, R., Sutherland, A., Bacharier, L.B., Beigelman, A., Busse, P., Frazier, A., Sette, A., 2020. IgE and T cell reactivity to a comprehensive panel of cockroach allergens in relation to disease. Front. Immunol. 11, 621700.
Powell, R.J., Frew, A.J., Corrigan, C.J., Durham, S.R., 2007. Effect of grass pollen immunotherapy with Alutard SQ on quality of life in seasonal allergic rhinoconjunctivitis. Allergy 62, 1335–1338.
Prangtaworn, P., Chaisri, U., Seesuay, W., Mahasongkram, K., Onlamoon, N., Reamtong, O., Tungtrongchitr, A., Indrawattana, N., Chaicumpa, W., Sookrung, N., 2018. Tregitope-linked refined allergen vaccines for immunotherapy in cockroach allergy. Sci. Rep. 8, 15480.
Prangtaworn, P., Mahasongkram, K., Saeung, A., Chaisri, U., Seesuay, W., Reamtong, O., Tungtrongchitr, A., Chaicumpa, W., Sookrung, N., 2021. A component-resolved therapeutic vaccine for cockroach allergy made of per a 9 and transforming growth factor-beta homologue, an immunosuppressive protein of Brugia malayi. Front. Immunol. 12, 676558.
Rabito, F.A., Carlson, J.C., He, H., Werthmann, D., Schal, C., 2017. A single intervention for cockroach control reduces cockroach exposure and asthma morbidity in children. J. Allergy Clin. Immunol. 140, 565–570.
Reed, S.G., Orr, M.T., Fox, C.B., 2013. Key roles of adjuvants in modern vaccines. Nat. Med. 19, 1597–1608.
Roberts, G., Pfaar, O., Akdis, C.A., Ansotegui, I.J., Durham, S.R., Gerth van Wijk, R., Halken, S., Larenas-Linnemann, D., Pawankar, R., Pitsios, C., Sheikh, A., Worm, M., Arasi, S., Calderon, M.A., Cingi, C., Dhami, S., Fauquert, J.L., Hamelmann, E., Hellings, P., Jacobsen, L., Knol, E.F., Lin, S.Y., Maggina, P., Mosges, R., Oude Elberink, J.N.G., Pajno, G.B., Pastorello, E.A., Penagos, M., Rotiroti, G., Schmidt-Weber, C.B., Timmermans, F., Tsilochristou, O., Varga, E.M., Wilkinson, J.N., Williams, A., Zhang, L., Agache, I., Angier, E., Fernandez-Rivas, M., Jutel, M., Lau, S., van Ree, R., Ryan, D., Sturm, G.J., Muraro, A., 2018. EAACI guidelines on allergen immunotherapy: allergic rhinoconjunctivitis. Allergy 73, 765–798.
Rosenstreich, D.L., Eggleston, P., Kattan, M., Baker, D., Slavin, R.G., Gergen, P., Mitchell, H., McNiff-Mortimer, K., Lynn, H., Ownby, D., Malveaux, F., 1997. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. N. Engl. J. Med. 336, 1356–1363.
Royer, C.M., Rudolph, K., Dietsch, G.N., Hershberg, R.M., Barrett, E.G., 2016. VTX-1463, a novel TLR-8 agonist, attenuates nasal congestion after ragweed challenge in sensitized beagle dogs. Immun. Inflamm. Dis. 4, 45–51.
Sadeghi, M., Koushki, K., Mashayekhi, K., Ayati, S.H., Keshavarz Shahbaz, S., Moghadam, M., Sankian, M., 2020. DC-targeted gold nanoparticles as an efficient and biocompatible carrier for modulating allergic responses in sublingual immunotherapy. Int. Immunopharmacol. 86, 106690.
Salari, F., Varasteh, A.R., Vahedi, F., Hashemi, M., Sankian, M., 2015. Down-regulation of Th2 immune responses by sublingual administration of poly (lactic-co-glycolic) acid (PLGA)-encapsulated allergen in BALB/c mice. Int. Immunopharmacol. 29, 672–678.
Satitsuksanoa, P., Globinska, A., Jansen, K., van de Veen, W., Akdis, M., 2018. Modified allergens for immunotherapy. Curr. Allergy Asthma Rep. 18, 9.
Scheiblhofer, S., Thalhamer, J., Weiss, R., 2018. DNA and mRNA vaccination against allergies. Pediatr. Allergy Immunol. 29, 679–688.
Schmitz, N., Dietmeier, K., Bauer, M., Maudrich, M., Utzinger, S., Muntwiler, S., Saudan, P., Bachmann, M.F., 2009. Displaying Fel d1 on virus-like particles prevents reactogenicity despite greatly enhanced immunogenicity: a novel therapy for cat allergy. J. Exp. Med. 206, 1941–1955.
Sehra, S., Yao, W., Nguyen, E.T., Glosson-Byers, N.L., Akhtar, N., Zhou, B., Kaplan, M.H., 2015. TH9 cells are required for tissue mast cell accumulation during allergic inflammation. J. Allergy Clin. Immunol. 136 (433–440), e431.
Sel, S., Wegmann, M., Sel, S., Bauer, S., Garn, H., Alber, G., Renz, H., 2007. Immunomodulatory effects of viral TLR ligands on experimental asthma depend on the additive effects of IL-12 and IL-10. J. Immunol. 178, 7805–7813.
Senti, G., Freiburghaus, A.U., Larenas-Linnemann, D., Hoffmann, H.J., Patterson, A.M., Klimek, L., Di Bona, D., Pfaar, O., Ahlbeck, L., Akdis, M., Weinfeld, D., Contreras-

Verduzco, F.A., Pedroza-Melendez, A., Skaarup, S.H., Lee, S.M., Cardell, L.O., Schmid, J.M., Westin, U., Dollner, R., Kundig, T.M., 2019. Intralymphatic immunotherapy: update and unmet needs. Int. Arch. Allergy Immunol. 178, 141–149.
Senti, G., Johansen, P., Haug, S., Bull, C., Gottschaller, C., Muller, P., Pfister, T., Maurer, P., Bachmann, M.F., Graf, N., Kundig, T.M., 2009. Use of A-type CpG oligodeoxynucleotides as an adjuvant in allergen-specific immunotherapy in humans: a phase I/IIa clinical trial. Clin. Exp. Allergy 39, 562–570.
Sever, M.L., Arbes Jr., S.J., Gore, J.C., Santangelo, R.G., Vaughn, B., Mitchell, H., Schal, C., Zeldin, D.C., 2007. Cockroach allergen reduction by cockroach control alone in low-income urban homes: a randomized control trial. J. Allergy Clin. Immunol. 120, 849–855.
Sharma, S., Nagar, E., Arora, N., 2022. Per a 5-derived T-cell peptides modulate NF-kB signalling to ameliorate allergic inflammation systemically in murine model of cockroach allergic hyper-reactivity. Clin. Exp. Immunol. 208, 292–300.
Shin, J.H., Kim, D.H., Kim, B.Y., Kim, S.W., Hwang, S.H., Lee, J., Kim, S.W., 2017. Anti-interleukin-9 antibody increases the effect of allergen-specific immunotherapy in murine allergic rhinitis. Allergy Asthma Immunol. Res 9, 237–246.
Simms, E.J., Syed, I., Rudulier, C., Larche, M., 2015. Peptide immunotherapy; short but long lasting? Curr. Treat. Options Allergy 2, 64–71.
Sola, J.P., Pedreno, Y., Cerezo, A., Penalver-Mellado, M., 2018. Development and characterization of an allergoid of cat dander for immunotherapy. Allergol. Immunopathol. 46, 491–498.
Sola Martinez, F.J., Barranco Jimenez, R.M., Martin Garcia, C., Senent Sanchez, C., Blanco Guerra, C., Fernandez-Rivas, M., Vega Castro, A., Davila Gonzalez, I., Carbonell Martinez, A., Panizo Bravo, C., Gomez Torrijos, E., Rodriguez Gil, D., Palacios Pelaez, R., 2020. Intradermal Phleum pratense allergoid immunotherapy. Double-blind, randomized, placebo-controlled trial. Clin. Exp. Allergy 50, 1352–1361.
Sookrung, N., Khetsuphan, T., Chaisri, U., Indrawattana, N., Reamtong, O., Chaicumpa, W., Tungtrongchitr, A., 2014. Specific B-cell epitope of per a 1: a major allergen of American cockroach (Periplaneta americana) and anatomical localization. Allergy Asthma Immunol. Res. 6, 325–332.
Sookrung, N., Reamtong, O., Poolphol, R., Indrawattana, N., Seesuay, W., Saelim, N., Tantilipikorn, P., Bunnag, C., Chaicumpa, W., Tungtrongchitr, A., 2018. Glutathione S-transferase (GST) of American cockroach, periplaneta americana: classes, isoforms, and allergenicity. Sci. Rep. 8, 484.
Srivastava, D., Gaur, S.N., Arora, N., Singh, B.P., 2011. Clinico-immunological changes post-immunotherapy with Periplaneta americana. Eur. J. Clin. Investig. 41, 879–888.
Srivastava, D., Mehta, A.K., Arora, N., Gaur, S.N., Singh, B.P., 2010. Proteolytically inactive per a 10 allergen of Periplaneta americana modulates Th2 response and enhances IL-10 in mouse model. J. Clin. Immunol. 30, 426–434.
Storni, F., Zeltins, A., Balke, I., Heath, M.D., Kramer, M.F., Skinner, M.A., Zha, L., Roesti, E., Engeroff, P., Muri, L., von Werdt, D., Gruber, T., Cragg, M., Mlynarczyk, M., Kundig, T.M., Vogel, M., Bachmann, M.F., 2020. Vaccine against peanut allergy based on engineered virus-like particles displaying single major peanut allergens. J. Allergy Clin. Immunol. 145, 1240-1253 e1243.
Sugiyama, T., Hoshino, K., Saito, M., Yano, T., Sasaki, I., Yamazaki, C., Akira, S., Kaisho, T., 2008. Immunoadjuvant effects of polyadenylic:polyuridylic acids through TLR3 and TLR7. Int. Immunol. 20, 1–9.
Tan, W., Zheng, J.H., Duong, T.M.N., Koh, Y.I., Lee, S.E., Rhee, J.H., 2019. A fusion protein of Derp2 allergen and flagellin suppresses experimental allergic asthma. Allergy Asthma Immunol. Res. 11, 254–266.
Thomsen, L.L., Topley, P., Daly, M.G., Brett, S.J., Tite, J.P., 2004. Imiquimod and resiquimod in a mouse model: adjuvants for DNA vaccination by particle-mediated immunotherapeutic delivery. Vaccine 22, 1799–1809.
Tsai, Y.G., Yang, K.D., Wen, Y.S., Hung, C.H., Chien, J.W., Lin, C.Y., 2019. Allergen-specific immunotherapy enhances CD8(+) CD25(+) CD137(+) regulatory T cells and decreases nasal nitric oxide. Pediatr. Allergy Immunol. 30, 531–539.
Tscheppe, A., Breiteneder, H., 2017. Recombinant allergens in structural biology, diagnosis, and immunotherapy. Int. Arch. Allergy Immunol. 172, 187–202.
Tscheppe, A., Palmberger, D., van Rijt, L., Kalic, T., Mayr, V., Palladino, C., Kitzmuller, C., Hemmer, W., Hafner, C., Bublin, M., van Ree, R., Grabherr, R., Radauer, C., Breiteneder, H., 2020. Development of a novel Ara h 2 hypoallergen with no IgE binding or anaphylactogenic activity. J. Allergy Clin. Immunol. 145, 229–238.
Uotila, R., Kukkonen, A.K., Greco, D., Pelkonen, A.S., Makela, M.J., 2019. Peanut oral immunotherapy increases IgG4 to Ara h 1, 2, and 6 but does not affect IgG4 to other allergens. Pediatr. Allergy Immunol. 30, 248–252.
Valdesoiro-Navarrete, L., Leon, M.E., Rodriguez, M., Indiveri, M., Ayats, R., Larramona, H., Gonzalez, M.G., de la Cruz, O.A., Garcia, M.B., 2022. Combination therapy of specific aeroallergens immunotherapy and omalizumab, in children with severe asthma. Allergol. Immunopathol. 50, 1–6.
Valenta, R., Karaulov, A., Niederberger, V., Zhernov, Y., Elisyutina, O., Campana, R., Focke-Tejkl, M., Curin, M., Namazova-Baranova, L., Wang, J.Y., Pawankar, R., Khaitov, M., 2018. Allergen extracts for in vivo diagnosis and treatment of allergy: is there a future? J. Allergy Clin. Immunol. Pract. 6 (1845–1855), e1842.
Wang, J., Hu, X., Xiang, D., 2018. Nanoparticle drug delivery systems: an excellent carrier for tumor peptide vaccines. Drug Deliv. 25, 1319–1327.
Wang, Y., McCusker, C., 2006. Neonatal exposure with LPS and/or allergen prevents experimental allergic airways disease: development of tolerance using environmental antigens. J. Allergy Clin. Immunol. 118, 143–151.
Weigt, H., Muhlradt, P.F., Larbig, M., Krug, N., Braun, A., 2004. The Toll-like receptor-2/6 agonist macrophage-activating lipopeptide-2 cooperates with IFN-gamma to reverse the Th2 skew in an in vitro allergy model. J. Immunol. 172, 6080–6086.
Wood, R.A., Togias, A., Wildfire, J., Visness, C.M., Matsui, E.C., Gruchalla, R., Hershey, G., Liu, A.H., O'Connor, G.T., Pongracic, J.A., Zoratti, E., Little, F., Granada, M., Kennedy, S., Durham, S.R., Shamji, M.H., Busse, W.W., 2014. Development of cockroach immunotherapy by the Inner-City Asthma Consortium. J. Allergy Clin. Immunol. 133 (846–852), e846.
Wurtzen, P.A., Gupta, S., Brand, S., Andersen, P.S., 2016. Grass pollen immunotherapy: where are we now. Immunotherapy 8, 399–411.
Yang, L., Zhu, R., 2017. Immunotherapy of house dust mite allergy. Hum. Vaccin. Immunother. 13, 2390–2396.
Zeltins, A., West, J., Zabel, F., El Turabi, A., Balke, I., Haas, S., Maudrich, M., Storni, F., Engeroff, P., Jennings, G.T., Kotecha, A., Stuart, D.I., Foerster, J., Bachmann, M.F., 2017. Incorporation of tetanus-epitope into virus-like particles achieves vaccine responses even in older recipients in models of psoriasis, Alzheimer's and cat allergy. NPJ Vaccine 2, 30.
Zhang, Z., Li, X.M., Li, Z., Lin, H., 2021. Investigation of glycated shrimp tropomyosin as a hypoallergen for potential immunotherapy. Food Funct. 12, 2750–2759.
Zhou, B., Ensell, M., Zhou, Y., Nair, U., Glickstein, J., Kermany, M.H., Cai, Q., Cai, C., Liu, W., Deng, Y.P., Kakigi, A., Barbieri, M., Mora, M., Kanangat, S., Yoo, T.J., 2012a. Prevention and treatment of DNA vaccine encoding cockroach allergen Bla g 1 in a mouse model of allergic airway inflammation. Allergy 67, 166–174.
Zhou, B., Yuan, J., Zhou, Y., Yang, J., James, A.W., Nair, U., Shu, X., Liu, W., Kanangat, S., Yoo, T.J., 2012b. The attenuation of cockroach allergy by DNA vaccine encoding cockroach allergen Bla g 2. Cell. Immunol. 278, 120–124.
Zieglmayer, P., Focke-Tejkl, M., Schmutz, R., Lemell, P., Zieglmayer, R., Weber, M., Kiss, R., Blatt, K., Valent, P., Stolz, F., Huber, H., Neubauer, A., Knoll, A., Horak, F., Henning, R., Valenta, R., 2016. Mechanisms, safety and efficacy of a B cell epitope-based vaccine for immunotherapy of grass pollen allergy. EBioMedicine 11, 43–57.
Zielen, S., Gabrielpillai, J., Herrmann, E., Schulze, J., Schubert, R., Rosewich, M., 2018. Long-term effect of monophosphoryl lipid A adjuvanted specific immunotherapy in patients with grass pollen allergy. Immunotherapy 10, 529–536.
Zimmer, J., Bonertz, A., Vieths, S., 2017. Quality requirements for allergen extracts and allergoids for allergen immunotherapy. Allergol. Immunopathol. 45 (Suppl 1), 4–11.
Zuidmeer-Jongejan, L., Huber, H., Swoboda, I., Rigby, N., Versteeg, S.A., Jensen, B.M., Quaak, S., Akkerdaas, J.H., Blom, L., Asturias, J., Bindslev-Jensen, C., Bernardi, M. L., Clausen, M., Ferrara, R., Hauer, M., Heyse, J., Kopp, S., Kowalski, M.L., Lewandowska-Polak, A., Linhart, B., Maderegger, B., Maillere, B., Mari, A., Martinez, A., Mills, E.N., Neubauer, A., Nicoletti, C., Papadopoulos, N.G., Portoles, A., Ranta-Panula, V., Santos-Magadan, S., Schnoor, H.J., Sigurdardottir, S. T., Stahl-Skov, P., Stavroulakis, G., Stegfellner, G., Vazquez-Cortes, S., Witten, M., Stolz, F., Poulsen, L.K., Fernandez-Rivas, M., Valenta, R., van Ree, R., 2015. Development of a hypoallergenic recombinant parvalbumin for first-in-man subcutaneous immunotherapy of fish allergy. Int. Arch. Allergy Immunol. 166, 41–51.