Allergen immunotherapy: past, present and future

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Abstract | Allergen immunotherapy is a form of therapeutic vaccination for established IgE-mediated hypersensitivity to common allergen sources such as pollens, house dust mites and the venom of stinging insects. The classical protocol, introduced in 1911, involves repeated subcutaneous injection of increasing amounts of allergen extract, followed by maintenance injections over a period of 3 years, achieving a form of allergen-specific tolerance that provides clinical benefit for years after its discontinuation. More recently, administration through the sublingual route has emerged as an effective, safe alternative. Oral immunotherapy for peanut allergy induces effective 'desensitization' but not long-term tolerance. Research and clinical trials over the past few decades have elucidated the mechanisms underlying immunotherapy-induced tolerance, involving a reduction of allergen-specific T helper 2 (T_H2) cells, an induction of regulatory T and B cells, and production of IgG and IgA 'blocking' antibodies. To better harness these mechanisms, novel strategies are being explored to achieve safer, effective, more convenient regimens and more durable long-term tolerance; these include alternative routes for current immunotherapy approaches, novel adjuvants, use of recombinant allergens (including hypoallergenic variants) and combination of allergens with immune modifiers or monoclonal antibodies targeting the T_H2 cell pathway.

Allergy is a growing problem that affects up to one in three of the population of westernized countries[1]. For example, the prevalence of physician-diagnosed allergic rhinitis has been estimated at 13% in children[2] and 14% in adults[3] in the USA and 23% in adults[4] in Europe. Allergic rhinitis often has a major impact on sleep quality, work or school performance and leisure activities and is frequently associated with comorbid asthma[5]. General allergic reactions following Hymenoptera stings have been estimated to occur in 3.4% of children and 7.5% of adults in Europe[6]. Although diagnostic criteria vary, a convincing history of food allergy with or without a physician diagnosis was found in 8% of children in the USA, 2% of whom were allergic to peanut[7]. The associated risks of anaphylaxis and occasional fatalities have a major impact on well-being and quality of life for patients and their families. Allergen avoidance, although representing optimal management for allergic diseases, is not often feasible and symptomatic treatment with anti-allergic medication may only be partially effective.

Allergen immunotherapy involves the repeated administration of allergen extracts or products over several years[8–10], and may offer a more permanent solution to drugs that only treat symptoms and not the underlying cause. Immunotherapy is offered to individuals who are atopic with IgE-mediated allergic rhinitis and/or allergic asthma due to inhaled allergens, such as pollens and house dust mites (HDMs), who have shown an inadequate response to anti-allergy drugs or who have experienced unacceptable drug side effects. Subcutaneous immunotherapy can be offered to patients who are at risk of anaphylaxis from insect stings[6]. Oral immunotherapy for allergy to foods has been an experimental approach[11]. However, for peanut allergy, there is now an approved oral peanut product for use in clinical practice[12,13].

In this Perspective, we review the insights gained from past experiences in allergen immunotherapy into the mechanisms of allergic inflammation and immunotherapy-induced tolerance. We describe how current practice has evolved to include both subcutaneous and sublingual routes, and to establish safer and more convenient approaches and to improve patient adherence to immunotherapy. We describe the ways in which current approaches may be further improved in the future owing to advances in molecular allergology, alternative routes of allergen administration and the potential for effective combination of allergen immunotherapy with immune modifiers or monoclonal antibodies that target the allergy-associated T helper 2 (T_H2) cell pathway.

Brief history of allergen immunotherapy

A timeline of key milestones in allergen immunotherapy is shown in FIG. 1. In 1911, Leonard Noon was the first to show that repeated injections of crude grass pollen extract into individuals with hay fever reduced immediate conjunctival sensitivity to grass pollen[14]. Freeman reported that during the following pollen season, they had reduced symptoms of rhinitis and asthma[15]. Noon's rationale is not clear, although grass pollen had been recognized as the causal agent in hay fever[16] and the concept may have evolved from the parallel development of prophylactic vaccination using killed or modified causal organisms for the prevention of infectious diseases (see https://historyofvaccines.org/history/vaccine-timeline/timeline).

In the first double-blind trial, Frankland in 1954 confirmed the efficacy of subcutaneous grass pollen injection therapy[17] for seasonal asthma, and showed that the activity responsible for the effect was contained within the high molecular weight protein-containing component of the allergen extract rather than the eluted low molecular weight fractions. Lowell and Franklin[18] subsequently demonstrated the efficacy of subcutaneous ragweed pollen extract contained within a multi-allergen mixture. In 1978, Norman and Lichtenstein were the first to demonstrate that allergen immunotherapy was allergen-specific,

in that a ragweed pollen extract was effective at relieving symptoms in dual-IgE-sensitized individuals during the ragweed season, but not during the ensuing grass pollen season[19]. In the same year, Hunt et al. demonstrated the efficacy of subcutaneous purified Hymenoptera venom immunotherapy, in contrast to a whole insect body extract, when compared with placebo in patients with severe insect venom hypersensitivity[20].

Remarkably, subcutaneous immunotherapy has changed little over the past 100 years, still involving weekly injections followed by monthly maintenance injections over several years. In 1998, a position paper by the World Health Organization (WHO) summarized the evidence for efficacy and identified the risks, particularly in individuals with uncontrolled asthma[8]. The report acknowledged progress in the use of more standardized allergen extracts, according to their purification and content of major allergens, and referred to emerging evidence for sublingual immunotherapy as a safer alternative route. This was later supported in a World Allergy Organization position paper on sublingual immunotherapy[9]. Venom immunotherapy has been established as a highly effective treatment in preventing anaphylaxis following insect stings[6].

In 1999, it was reported that 3 years of continuous subcutaneous immunotherapy with grass pollen extract resulted in long-term benefits for 3 years after its discontinuation[21]. Reproduced on several occasions since[22,23], this key observation confirmed the allergen specificity and long-term disease-modifying effects of allergen immunotherapy. Allergen immunotherapy has provided a unique human model to study immunological events underlying long-term antigen-specific tolerance. Randomized controlled trials that have confirmed long-term clinical efficacy after discontinuation are summarized in Supplementary Table S1.

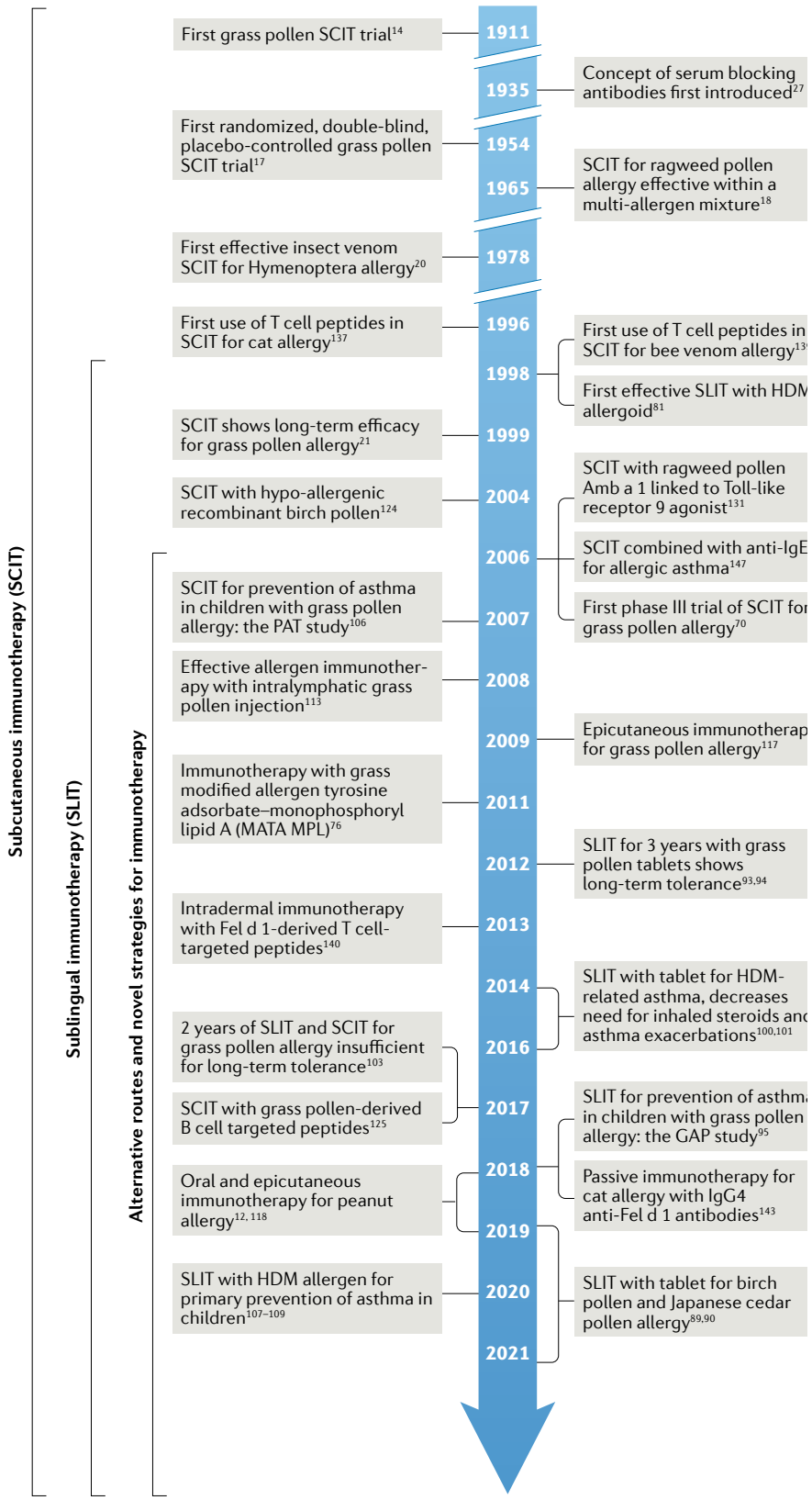


Fig. 1 | **Key milestones in allergen immunotherapy.** HDM, house dust mite.

Understanding immune tolerance by allergen immunotherapy

Mechanisms of immunotherapy for allergy to inhalant allergens. In individuals with atopic allergy, natural exposure to low concentrations of environmental allergens results in allergic inflammation involving IgE-mediated activation of mast cells and tissue eosinophilia, events under the regulation of T_H2-type cytokines (FIG. 2). In 1921, Prausnitz and Kutsner[24] were the first to demonstrate the passive transfer by a serum factor (referred to as 'reagin' and, subsequently in 1966, characterized as IgE[25,26]) of immediate cutaneous IgE sensitivity. In 1935 Cooke and colleagues showed that 'protective immunity' after allergen immunotherapy could also be transferred passively[27]. They showed that serum obtained after immunotherapy from individuals with ragweed pollen hay fever, when injected intradermally into sensitized

untreated controls, could block the immediate cutaneous response to ragweed pollen. These two observations illustrated for the first time that hypersensitivity (allergy) and protective immunity (immunotherapy) were dependent on passively transferable serum factors that were subsequently identified as allergen-specific IgE and allergen-specific IgG/IgA-associated IgE-blocking activity, respectively.

Administration of high doses of allergen either by injection or sublingually during immunotherapy results in the induction of dendritic cells with a pro-regulatory phenotype (tolerogenic dendritic cells)[28,29]. Within weeks, there is preferential induction of peripherally derived regulatory T (T_{reg}) cells that express IL-10 (REFS.[30–32]), transforming growth factor-β (TGFβ)[33] and IL-35 (REF.[34]), and thymus-derived $FOXP3^+$ T_{reg} cells[32]. These cells are detectable in the circulation and nasal mucosa[35,36] following pollen immunotherapy. T_{reg} cells inhibit the differentiation of T_H2 cells via regulatory cytokines as well as by cell–cell interactions[37]. IL-10 induces B cells to undergo isotype class switching in favour of allergen-specific IgG subclasses including IgG1 (REF.[38]) and IgG4 (REF.[35]), whereas TGFβ induces preferential switching of B cells to produce IgA[39]. These B cells differentiate into plasma cells that synthesize and release allergen-specific IgG1, IgG4, IgA1 or IgA2, which is detectable in the peripheral blood and nasal fluid following immunotherapy[40]. Allergen-specific IgG and IgA compete with IgE for allergen and directly inhibit the formation of allergen–IgE complexes[41], although the blocking activity of IgA relative to IgG has recently been questioned[42]. These 'blocking antibodies' inhibit IgE-dependent activation of mast cells and basophils[43]. They also inhibit the IgE-facilitated presentation of allergen to low-affinity receptor for IgE (FcεRII)-expressing B cells and to high-affinity IgE receptor (FcεRI)-expressing dendritic cells, with a resulting decrease in T_H2 cell development[44] (FIG. 2).

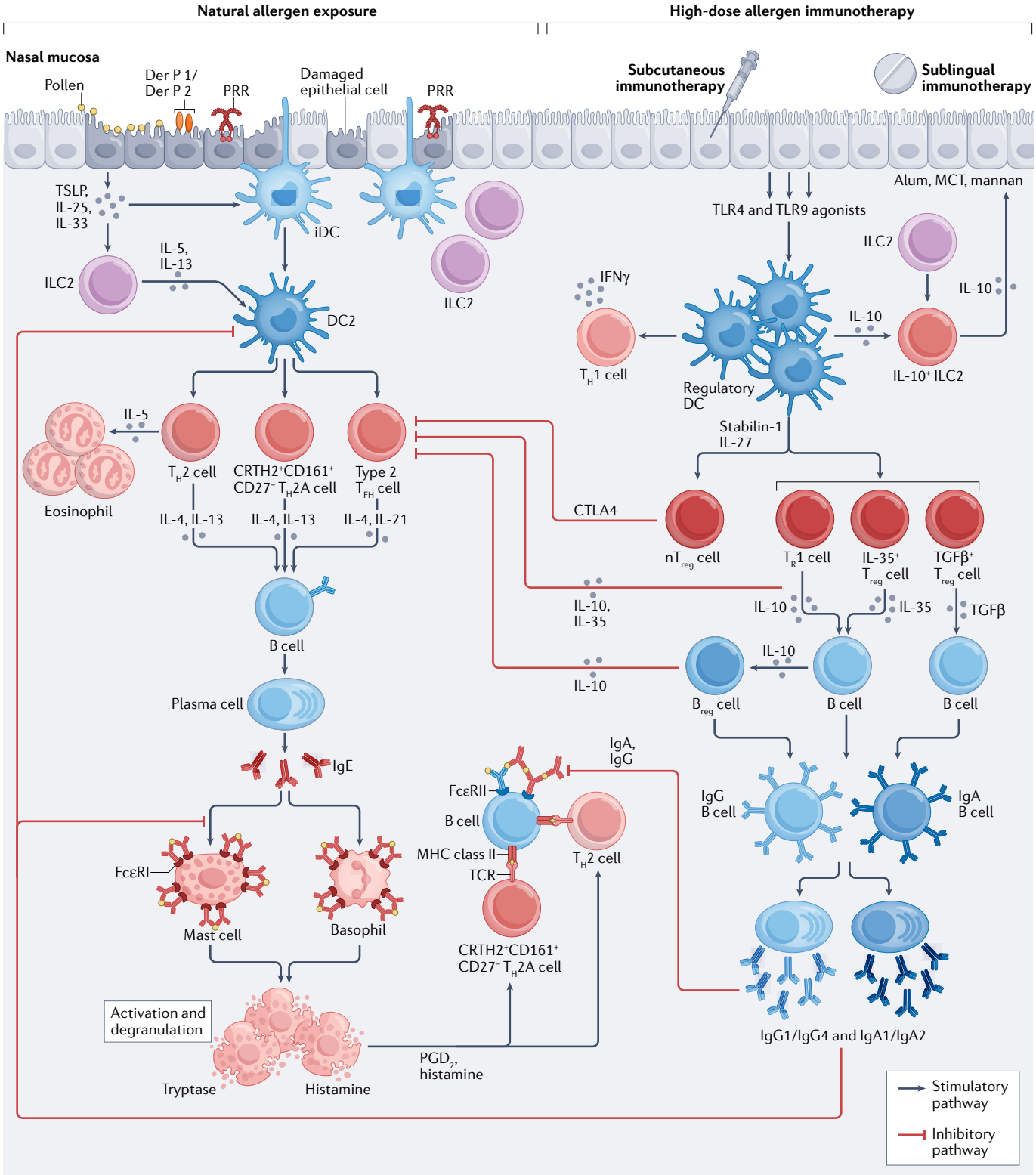
T_{reg} cells are induced by allergen-primed regulatory dendritic cells within weeks of starting allergen immunotherapy[31,32]. By contrast, high-dose allergen exposure, possibly via presentation by non-professional antigen presenting cells, initiates a more delayed immune deviation in favour of allergen-driven T_H1 cell responses[32,45] that has been detected at 12 months in the blood and target organs. By in situ hybridization of skin biopsies, local increases in IL-12-producing macrophages and interferon-γ-producing T cells following intradermal allergen challenge were accompanied by decreases in skin IL-4-producing T cells and improvement in clinical symptoms[46].

Under the regulation of epithelial cytokines, group 2 innate lymphoid cells (ILC2s), although unable to respond directly to antigen, represent an alternative source of T_H2-type cytokines to amplify and augment local allergic inflammation[47]. Grass pollen allergen immunotherapy has been shown to inhibit seasonal increases in ILC2s (REF.[48]) and to induce a phenotypically distinct subset of ILC2s that express surface KLRG1 and secrete IL-10[49]. Distinct subsets of regulatory B cells (B_{reg} cells)[50,51] and regulatory T_{reg} cells[52] also increase and provide further sources of IL-10 after immunotherapy.

Mechanisms of oral immunotherapy for peanut allergy. Compared with immunotherapy for inhalant allergy, immunotherapy for food allergy[53] is less well studied, with the exception of peanut allergy for which there is now an approved oral product comprising 300 mg encapsulated whole peanut (AR101) administered daily (the PALISADE study)[12]. As for grass pollen immunotherapy, successful desensitization to peanut allergen was accompanied by a marked reduction in allergen-stimulated effector memory T cells with a T_H2 cell phenotype (characterized as $CRTH2^+CD161^+CD27^-$ and referred to as T_H2A cells)[54,55]. The mechanism of this decrease in peripheral T_H2A cells is unknown. Whereas earlier studies of peanut oral immunotherapy showed transient increases in peripheral blood mononuclear cell IL-10 secretion and increases in $CD25^+FOXP3^+$ T cells[56], this could represent memory effector T cell activation, and subsequent detailed flow cytometry analysis in the PALISADE study failed to show that marked decreases in allergen-stimulated T_H2A cells were accompanied by increases in peripheral T_{reg} cells[55], although this does not exclude the possibility of local T_{reg} cell induction in the gut. For example, in a mouse model of food allergy, the mucosal induction of $FOXP3^+$ T_{reg} cells depends on local $CD103^+$ dendritic cell activation and involves retinoic acid pathways and secretion of TGFβ rather than IL-10 (REF.[57]). Individuals with peanut allergy have a higher level of allergen-stimulated basophil activation than IgE-sensitized but non-allergic controls[55,58]. A striking finding during peanut oral immunotherapy was an early decrease in basophil activation (as indicated by decreased surface CD203c levels) that was accompanied by transient increases in peanut-specific IgE and marked increases in the IgG4 to IgE ratio[55] and a decrease in functional IgE-binding assays[56].

In contrast to inhalant allergen immunotherapy, oral peanut immunotherapy has not shown convincing evidence of long-term efficacy[13,53]. Prolonged administration over 2 years in children and young adults (the POISED study[59]) and over 2.5 years in young children (aged 1–4 years, the IMPACT study[60]), using high maintenance doses (4,000 mg oral peanut daily), was highly effective in inducing desensitization, but sustained unresponsiveness was only observed at 3 years (12 and 6 months after discontinuation) in 13% and 21% of participants, respectively. However, those who did develop sustained unresponsiveness had lower baseline levels of peanut-specific IgE and of basophil activation, had higher specific IgG4 to IgE ratios and were younger (particularly when initiated in children younger than 1 year old) compared with those who did not. Possible explanations for these findings are the potency of peanut allergen in inducing multivalent and high-affinity IgE responses to conformational rather than linear epitopes[61], accompanied by exuberant T_H2A cell responses that recur rapidly after immunotherapy is discontinued, and/or absence of effective modulation by sustained antigen-specific T_{reg} cell responses[55].

Mechanisms of immunotherapy for allergy to venoms. The availability of purified venom allergens in the 1990s enabled the study of immunological mechanisms of venom allergy in the absence of lipopolysaccharide contamination of crude allergen extracts. Following successful subcutaneous immunotherapy with purified bee venom allergen, stimulation of peripheral blood mononuclear cells with phospholipase A2 (PLA2; a major bee venom allergen) demonstrated reduced allergen-specific T cell proliferation and T_H2-type and T_H1-type cytokine production[62] and induction of IL-10-producing T_{reg} cells[30,63]. With venom immunotherapy, a rapid desensitization has been shown to be effective and safe using accelerated subcutaneous immunotherapy protocols ('rush' and 'ultra-rush' protocols)[64]. A striking early event, within hours or days of immunotherapy administration, was the desensitization of basophils by immune silencing of FcεRI-activated basophils, mediated by histamine 2 receptor (HR2)[65], resulting in inhibition of basophil mediator release including histamine, sulfidopeptide



leukotrienes and cytokines. The differential regulation of histamine receptor subtypes on T cells was also shown to be important in the development of IL-10-producing T_{reg} cells, with an increased HR2 to HR1 ratio favouring the development of IL-10-producing T_{reg} cells[66,67]. Subsequent studies of venom immunotherapy highlighted a critical role for the induction of a distinct subset of PLA2-specific regulatory B (B_{reg}) cells[50] that produced both IL-10 and allergen-specific IgG4. Allergen-specific IgG4 and IgE-blocking activity was demonstrable in beekeepers exposed to repeated natural stings as well as during successful venom immunotherapy[68,69]. However, in contrast to immunotherapy with inhalant allergens, following withdrawal of venom immunotherapy there was persistent suppression of allergen-specific IgE responses in the absence of persisting IgG-associated IgE-blocking activity[69], implying distinct mechanisms of long-term tolerance. Overall, these studies highlight

◀ Fig. 2 | **Mechanisms of allergic inflammation and immunotherapy.** Allergic inflammation involves IgE-dependent activation of mast cells and local tissue eosinophilia[159] under the regulation of T helper 2 (T_H2)-type cytokines (IL-4, IL-5, IL-9 and IL-13). The innate immune system, including specialized subsets of dendritic cells[28] and innate lymphoid cells (ILCs)[47], has a role in both induction and regulation of allergen-induced T_H2-type responses. These innate cells are under the influence of epithelial cell-derived cytokines including thymic stromal lymphopoietin (TSLP)[160], IL-25 and IL-33. In individuals with atopic allergy, type 2 dendritic cells[28] (DC2s) preferentially induce the differentiation of T_H2 cells and a population of allergen-stimulated T_H2 cells defined by high expression of CRTH2 and CD161 and low expression of CD27 ($CRTH2^+CD161^+CD27^-$; referred to as T_H2A cells). A further subset of cells expressing T_H2-type cytokines are type 2 T follicular helper (T_{FH}) cells[161], which derive from the marginal zones of lymph nodes. Allergen–IgE cross-linking of adjacent high-affinity IgE receptor (FcεRI) receptors on mast cells releases granule-derived mediators, such as tryptase and histamine, and membrane-associated lipid mediators that include prostaglandin D2 (PGD_2) and sulfidopeptide leukotrienes[162]. Allergen–IgE complexes also bind to surface low-affinity receptor for IgE (FcεRII) on B cells that results in IgE-facilitated T_H2 cell development[41,163]. During subcutaneous immunotherapy and sublingual immunotherapy, high-dose allergen exposure restores regulatory dendritic cells[28,29] that produce IL-10 (REFS. [30,31]) and IL-12 (REFS. [32,46]), inhibits T_H2 cell responses[104,164] and promotes regulatory T (T_{reg}) cell[30,34] and regulatory B (B_{reg}) cell[50,51] responses and immune deviation in favour of a T_H1 cell response[32,45]. There is preferential B cell isotype switching towards IgG and IgA[104,105], resulting in IgE-blocking activity[41,163,165], which inhibits both IgE-mediated activation of mast cells and basophils and IgE-facilitated antigen presentation and T_H2 cell responses[44,163]. Red arrows indicate suppressive activities of T_{reg} cells and B_{reg} cells, and IgG/IgA-associated IgE blocking activity. CTLA4, cytotoxic T lymphocyte antigen 4; iDC, immature dendritic cell; MCT, microcrystalline tyrosine; nT_{reg} cell; thymus-derived natural regulatory T cell; PRR, pattern recognition receptor; TCR, T cell receptor; TGFβ, transforming growth factor-β; TLR, Toll-like receptor; T_R1 cell, type 1 regulatory T cell (characterized by the co-expression of CD49b and LAG3) [166].

the importance in venom immunotherapy of rapid early desensitization of basophils, differential expression of histamine receptors on effector cells and T cells and the role of B_{reg} cells as an alternative source of IL-10 and IgG4. There is persistent IgE suppression, rather than a prolonged IgG-associated IgE-blocking activity, following discontinuation of venom immunotherapy[68].

Insights from the past 20 years

Although regarded as the gold standard[8,9,70], allergen immunotherapy given by subcutaneous injection requires specialist supervision owing to the risk of allergic side effects including anaphylaxis. In the USA, allergen extracts are prepared in 50% glycerin, which acts as a preservative and stabilizer, whereas in Europe extracts are alum-precipitated, which slows the release of allergen on injection and reduces immediate allergic side effects[71]. In recent years, there have been attempts to improve the safety and convenience for patients whilst retaining efficacy of allergen immunotherapy. These include the use of modified allergens (known as allergoids) and alternative routes of immunotherapy, as discussed below. FIGURE 3 summarizes the current and novel approaches for allergen immunotherapy.

Modified allergens. Chemical modification of allergens by use of glutaraldehyde or formaldehyde to produce allergoids[72,73], with altered tertiary structure and reduced allergenicity, has shown modest efficacy but no obvious benefits over standard extracts in terms of reduced allergic side effects. This unaltered risk of side effects from allergoids could be due to retained IgE epitopes, the exposure of previously latent IgE epitopes or the acquisition of novel IgE epitopes during processing. Similarly, the production of 'medium length peptides' from allergens, either by controlled hydrolysis[74] or synthetic[75] peptides based on the known sequences of major allergens, retains the capacity to generate protective IgG responses and has reduced ability to induce human basophil activation in vitro. These approaches have used shorter treatment regimens, for example with three to six pre-seasonal injections for pollen allergy[76]. It is therefore not surprising that they have shown only modest efficacy at best and no advantages in terms of safety compared with more prolonged courses over several years using conventional standardized allergen extracts. There have been no head to head comparisons with these approaches and conventional allergen extracts. (Recombinant allergen mixtures and hypoallergenic variants are discussed in 'Novel immunotherapy strategies'.)

Sublingual immunotherapy. Following the failure of oral immunotherapy for inhalant allergens[77], possibly due to gastric digestion of allergens, sublingual immunotherapy was considered as a way of directly accessing local lymphoid tissue and the regional draining lymph nodes shared by the upper respiratory tract. The oral mucosa was known to be an immunologically privileged site as reflected by tolerance to daily exposure to high levels of food proteins without developing hypersensitivity in the vast majority of individuals[78]. Furthermore, there are high levels of dendritic cells and fewer mast cells in the oral mucosa compared with other mucosal surfaces[79]. Moreover, the sublingual route was shown to be effective in inducing allergen-specific tolerance in mouse models[80].

Studies of allergic rhinitis in humans have shown sublingual immunotherapy to be an effective and safe alternative to subcutaneous immunotherapy[9,81]. The treatment involves placing allergen extracts daily, in liquid[82–84] or tablet[85,86] form, under the tongue and can be self-administered following medical supervision of the first dose[9]. Systematic reviews and meta-analyses have confirmed efficacy of pre-seasonal or co-seasonal immunotherapy for seasonal rhinitis and continuous treatment for perennial rhinitis due to HDM allergens[87]. Recent adequately powered randomized controlled trials of sublingual tablets have shown consistent efficacy in seasonal allergic rhinitis due to grass[85,86], ragweed[88], birch[89] and Japanese cedar[90] pollen allergy. The effect size of the treatment on symptoms and/or use of rescue medication is consistently 30–40% better than placebo treatment, similar to that observed in a phase 3 trial of subcutaneous immunotherapy with grass pollen extract, and compares favourably with the World Allergy Organization's proposed minimal important difference for clinical efficacy of 20%[91]. Indirect meta-analysis of sublingual tablet treatment compared with pharmacotherapy revealed efficacy greater than antihistamine tablets and comparable with that observed with intranasal corticosteroids[92].

There are now three studies in adults[90,93,94] and one in children aged 5–12 years[95] that confirm that daily sublingual allergy tablet treatment for 3 years induces long-term clinical benefits for at least 2 years after stopping the treatment (see Supplementary Table 1). Sublingual tablet therapy given over 12 months for HDM-induced perennial rhinitis was shown to be effective in four separate studies[96–99]. Effect sizes were less than those observed for pollen sublingual immunotherapy, around 17–20% compared with placebo, possibly related to difficulty in selecting those HDM-IgE-sensitized individuals in whom HDM was causal, rather than other perennial non-allergic causes of rhinitis[96–99]. In HDM-induced allergic asthma, sublingual tablet

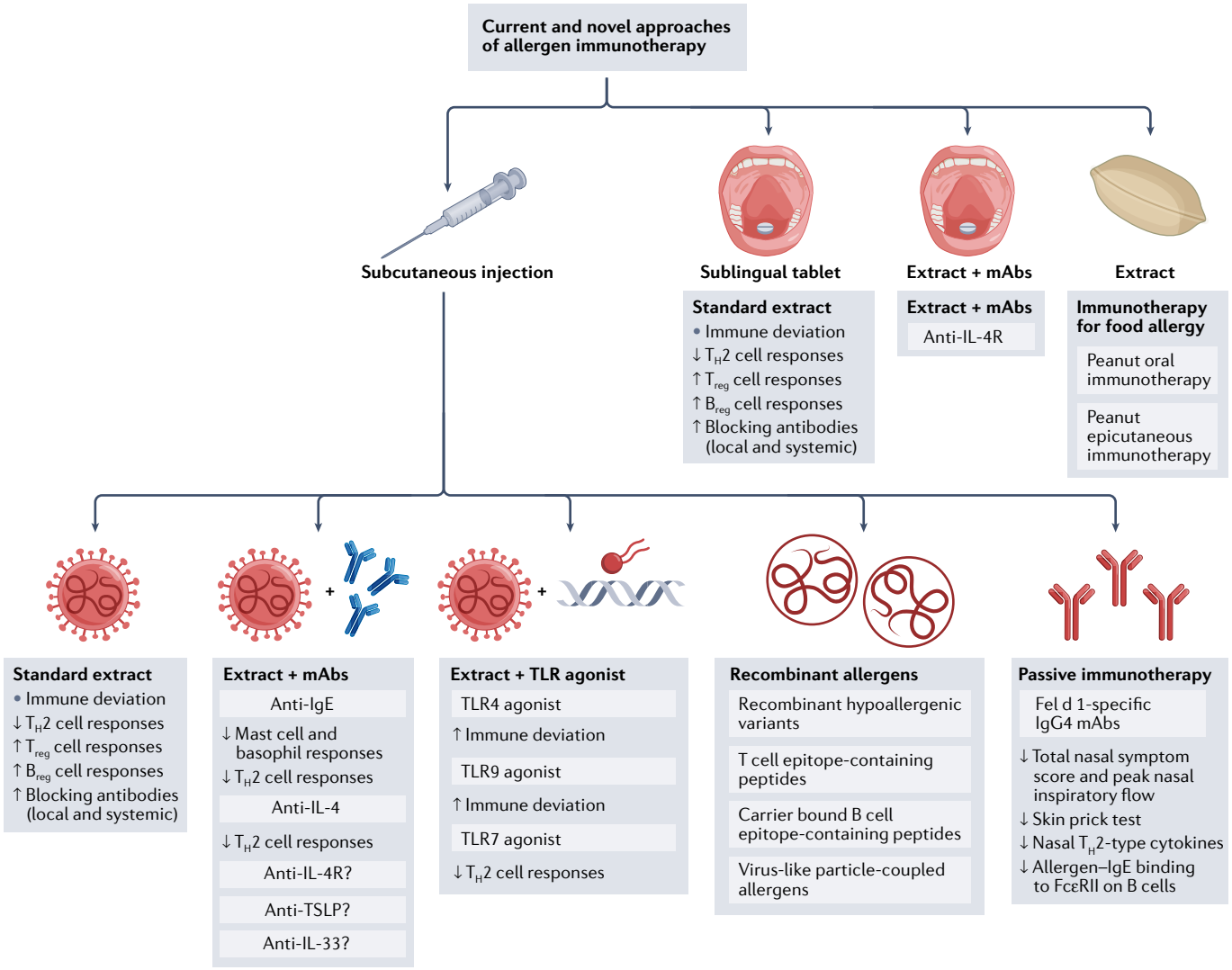


Fig. 3 | **Current and novel approaches of allergen immunotherapy.** At present, long-term tolerance for inhalant allergies may only be achieved by allergen immunotherapy with standardized whole allergen extracts via either subcutaneous or sublingual routes. To better harness the known underlying mechanisms, novel strategies are being explored to achieve safer, effective, more convenient regimens and more durable long-term tolerance. These include the combination of allergen extract with monoclonal antibodies (mAbs) directed against the T helper 2 (T_H2) cell pathway, or with immune modifiers such as Toll-like receptor (TLR) agonists. Molecular allergology has enabled more accurate allergy diagnosis and the development of recombinant whole allergens and hypoallergenic variants that, in the future, may result in a more individualized 'tailor-made' allergen immunotherapy. Allergen-derived peptides have been developed to target specifically underlying T or B cell-dependent pathways. These are likely to be safer, although so far they have not shown greater efficacy over whole allergen approaches that target both pathways. On the basis of the known ability of allergen immunotherapy to induce IgE-blocking antibodies, passive immunotherapy by injection of cocktails of IgG4 monoclonal antibodies directed against IgE epitopes of major allergens has proved successful in inhibiting human nasal allergen challenge responses. Oral immunotherapy in children with peanut allergy has been highly effective in inducing 'desensitization', whereas long-term tolerance remains elusive, and the treatment is accompanied by occasional serious systemic side effects. Earlier intervention in infancy and early childhood and/or the use of allergen combination strategies may overcome these problems. The epicutaneous approach using peanut allergen patches may be less effective in desensitization but is able to reduce the risk of anaphylaxis on exposure to traces of peanut and this may be a more feasible approach, with lower risk of treatment-related systemic side effects. B_{reg} cell, regulatory B cell; FcεRII, low-affinity receptor for IgE; IL-4R, interleukin-4 receptor; T_{reg} cell, regulatory T cell; TSLP, thymic stromal lymphopoietin.

immunotherapy reduced the requirement for inhaled corticosteroids[100] and decreased the rate of acute exacerbations of asthma[101]. HDM tablet immunotherapy has been approved for these indications in Europe and as an add-on treatment option for patients with HDM-triggered allergic asthma on low-to-high dose inhaled corticosteroids (https://ginasthma.org/reports/).

Subcutaneous versus sublingual allergen immunotherapy. The European Academy of Allergy and Clinical Immunology recently published evidence-based treatment guidelines that confirm the efficacy, safety and long-term benefits of subcutaneous and sublingual allergen immunotherapy for seasonal and perennial allergic rhinoconjunctivitis[102]. A recent clinical trial compared subcutaneous grass pollen immunotherapy and sublingual grass pollen tablet immunotherapy[103]. Both routes were effective in terms of the clinical response, but in contrast to 3 years of either treatment, 2 years of treatment was insufficient to maintain tolerance 1 year after stopping therapy. Flow cytometry confirmed that both routes suppressed allergen-specific T_H2 cell responses at 2 years that reversed at 3 years, along

with the loss of clinical efficacy. Similarly, suppression of T_H2-type cytokines (IL-4, IL-5, IL-9 and IL-13) in the nasal mucosa was reversed at 3 years[104]. By contrast, serum IgE-blocking activity, as reflected by inhibition of IgE-facilitated allergen–IgE binding to B cells and allergen-stimulated activation of basophils, was suppressed and this persisted throughout the 3 years. Blocking antibodies were present in both serum and nasal fluid. For subcutaneous immunotherapy, the IgE-inhibitory activity was predominantly mediated by IgG4, whereas for sublingual immunotherapy local nasal and systemic blocking antibodies were largely IgA1 and/or IgA2 (REF. [105]). Although speculative, these data support the idea that whereas suppression of T_H2-type responses is necessary for the induction of allergen-specific tolerance, prolonged alterations in the B cell compartment may be necessary for persistence of tolerance[104].

A secondary preventive role of immunotherapy in asthma was suggested by studies of both subcutaneous[106] and sublingual[95] immunotherapy in children aged 5–12 years with seasonal rhinitis, in whom 3 years of treatment reduced both symptoms of asthma and requirements for asthma medication at 5 years.

Primary prevention of inhalant allergies in infants has been tested in pilot studies[107,108]. A placebo-controlled trial of HDM sublingual drops was performed in infants, aged 6–18 months, at high risk of developing allergy. There was a reduction in multiple allergen sensitizations[108], as determined by skin testing, and there appeared to be a reduction in asthma prevalence at 6 years[109]. Although preliminary, these data provide incentive for a larger prospective controlled trial of HDM immunotherapy for primary prevention of asthma in high-risk infants. Whereas whole allergen or recombinant wild type-like allergens boost IgE responses and have potential to induce IgE sensitization, modified allergen derivatives or hypoallergenic peptides are less likely to induce IgE[110,111] and may therefore hold more promise in the future for primary prevention.

Alternative routes of immunotherapy. Intralymphatic immunotherapy involves injecting allergen extracts into lymph nodes, generally in the groin, under ultrasound guidance[112]. The rationale for this approach is that targeting the immune system directly could more efficiently augment allergen presentation to T cells whilst avoiding direct mast cell activation. Small placebo-controlled trials have shown modest benefit using extracts derived from grass pollen[113] and tree pollen[114]. In a small study of participants with cat allergy[115], a recombinant cat Fel d 1 allergen was fused with a translocation sequence and a fragment of the human invariant chain to enhance immunogenicity. Three intralymphatic injections of the Fel d 1 fusion protein at 4-weekly intervals protected against nasal challenge with whole cat allergen extract compared with participants treated with placebo. Several studies have shown efficacy of a short course of injections via the intralymphatic route for grass pollen allergy[113,114,116], although this has not been confirmed in all studies[112].

Oral immunotherapy for inhalant allergens has not been effective[77], possibly because allergen extracts are degraded by gastric acid. By contrast, oral peanut immunotherapy is of proven efficacy in children, although it has a high prevalence of side effects. For example, in a phase 3 trial in children 4–17 years old[12], oral peanut administered as capsules achieved a predetermined threshold of response to peanut in 67.2% of participants treated with peanut compared with 4.0% of participants treated with placebo, but gastrointestinal side effects were common. Systemic allergic side effects occurred in 14.2% compared with 3.2% in patients treated with placebo, including one case of anaphylaxis. Despite effective desensitization induced by oral peanut immunotherapy[59], long-term tolerance, even at high doses with attendant side effects, has been elusive[13].

The epicutaneous route was developed to take advantage of the high numbers of resident dendritic cells in the skin to facilitate allergen processing of very low allergen concentrations[117]. Delivery of peanut extract via a skin patch to children (aged 4–11 years) with peanut allergy resulted in desensitization to oral peanut challenge in 35.3% of the children compared with 13.6% of participants treated with placebo and fewer side effects, which were largely confined to local application site reactions[118]. At present, peanut immunotherapy is not recommended for routine care outside specialist centres. However, early introduction of foods containing peanut for prevention of peanut allergy in infants has been remarkably effective[119]. Introduction of peanut at 4–6 months of age is now routinely recommended for infants with severe eczema or egg allergy who are at high risk of developing peanut allergy[120]. Similarly, oral peanut immunotherapy in children aged 1–4 years who are peanut sensitized and symptomatic has been shown to be effective and safer when introduced very early in the course of their disease, when there are very low levels of allergen-specific IgE antibodies[60].

Novel immunotherapy strategies

Molecular allergology. Most allergens contained within common inhalants and foods have now been cloned. This has enabled precise molecular diagnosis of IgE sensitivities to major allergens (recognized by more than 50% of individuals) and minor allergens and the identification of cross-reactive epitopes of less clinical relevance[121]. An accurate molecular diagnosis may assist an individually tailored selection of allergen extracts for immunotherapy that may translate into improved outcomes. There is also the opportunity for more precise monitoring of relevant IgE and IgG responses during treatment. DNA technology has enabled the production of recombinant allergens[122], recombinant mixtures[123] and hypoallergenic variants for immunotherapy[124,125] that precisely match the individual's sensitivities without the risk of IgE sensitization to irrelevant allergens[126]. However, although these recombinant vaccines and recombinant hypoallergenic variants have been effective in phase 2 trials[122,123], they have not so far shown added benefits in terms of efficacy or safety over currently available standardized allergen extracts[122]. A recombinant hypoallergenic variant targeting B cells to selectively produce IgG responses is discussed below[125].

DNA-based vaccines. DNA-based vaccines[127] have been tested in mouse models of allergy[127,128] and shown to induce preferential T_H1 cell and T_{reg} cell responses and downregulate T_H2 cell responses[129]. There are, however, reservations concerning their repeated use in humans based on theoretical risks of incorporation of plasmid DNA into the human genome inducing carcinogenesis, development of anti-DNA antibodies and the unknown effects of long-term allergen persistence with potential for widespread IgE triggering and risk of anaphylaxis[128]. One approach tested in patients with allergy to Japanese cedar pollen involved the incorporation of lysosomal-associated membrane protein 1 (LAMP1) into a plasmid vector encoding Cry j 2, a major allergen of Japanese cedar pollen. LAMP1 targets the plasmid to the lysosomal compartment to reduce the risk of release of free allergen from the cell and,

thereby, decrease the risk of anaphylaxis[130]. After four intramuscular injections at 2-weekly intervals, there was inhibition of the immediate skin test response to Cry j 2 at 4 months in 10 of 12 participants, but there was no information on other clinical outcomes.

Another DNA-based approach has been to combine allergen with bacterial DNA sequences that contain CpG motifs to selectively target Toll-like receptor 9 (TLR9) expressed on human B cells and dendritic cells. The major ragweed pollen allergen Amb a 1 covalently linked to a B-type CpG-containing oligodeoxynucleotide (ODN)[131] was successful in a phase 2 trial in ragweed pollen-induced hay fever, although this was not confirmed in a phase3 trial and the approach was discontinued. An alternative approach involved mixing HDM extract with an A-type CpG ODN (G10) encapsulated within a virus-like particle derived from the surface protein coat of bacteriophage Qb (QbG10)[132]. The aim of this approach was to protect against allergen IgE triggering, facilitate allergen uptake and co-stimulate TLR9 to enhance HDM-stimulated T_{reg} cell formation and/or T_H1-type immune deviation. In a phase 2 trial, six subcutaneous injections at intervals of 1-2 weeks of allergen-CpG ODN-loaded virus-like particles, when given to patients with allergic rhinoconjunctivitis, were effective in suppressing the immediate conjunctival response to HDM challenge. Paradoxically, QbG10 alone was as effective as the QbG10–HDM combination, suggesting that a direct effect of CpG ODN virus-like particles on the innate immune response may have been sufficient to block the allergen-specific response[132]. However, subsequent placebo-controlled trials of QbG10 alone in severe allergic asthma have yielded inconsistent results[133,134].

Finally, vaccines based on mRNA constructs have been successful in inducing type 1 immune deviation and suppressing allergic inflammation in mouse models of allergy[135]. Their success against SARS-CoV-2 in the COVID-19 pandemic will inevitably stimulate interest in whether mRNA vaccines may have a future role in treating allergic diseases.

Targeted approaches. An important question for allergen immunotherapy is whether novel strategies should target predominantly the T cell response with minimal or no risk of anaphylaxis[136] or, alternatively, target the predominant B cell response that favours generation of IgG and IgA responses with IgE-blocking potential[104].

Antigen-specific approaches targeting T cells have involved the use of short-chain T cell peptide combinations that have been developed based on in vitro human T cell epitope mapping of individual major allergens with a broad HLA-restriction repertoire to enable peptide recognition by most of the targeted allergic population. The aim has been to selectively drive 'protective' T cell responses in the absence of significant IgG antibody responses[136–138]. Although minimizing the risk of IgE-mediated anaphylaxis, there is the possibility of inducing T cell-dependent late-phase asthmatic responses. In a pilot study, patients with a history of bee venom allergy received increasing doses of a mixture of three T cell epitope peptides of PLA2 subcutaneously over 2 months. Whereas all five treated participants were able to tolerate an intracutaneous challenge with PLA, two of the five developed systemic reactions after a live bee sting challenge, implying incomplete protection[139]. In patients with cat allergy, a mixture of 7 Fel d 1 peptides (comprising 13–17 amino acids) administered intradermally at intervals of 2–4 weeks over 12 weeks reduced rhinoconjunctivitis symptom scores in an environmental challenge chamber during controlled exposure to whole cat allergen. At 1 year, there was a marked reduction in symptoms that suggested induction of long-term clinical tolerance[140]. However, a phase 3 field trial of Fel d 1 peptide immunotherapy (ClinicalTrials.gov, NCT01620762)[141] was unsuccessful. This may have been due to an observed high placebo response in the control population or selection of cat owners (as opposed to cat avoiders) who may already have exhibited a degree of tolerance due to natural allergen exposure. Following a further unsuccessful phase 3 trial of immunotherapy with HDM-derived T cell peptide (NCT02150343)[142] the programme was halted.

Selective targeting of B cell responses during allergen immunotherapy is supported by the detection of blocking antibodies during conventional allergen immunotherapy[27,40] and by recent studies identifying increases in IL-10-producing B_{reg} cells during immunotherapy for bee venom[50] and HDM allergies[51]. This concept receives further support from a trial of passive immunization in individuals with cat allergy. A single subcutaneous injection of a mixture of two recombinant anti-Fel d 1 antibodies conferred protection against nasal challenge with whole cat allergen extract that persisted for almost 3 months[143]. There was a reduction in nasal fluid T_H2-type cytokines and accompanying increases in serum and nasal IgE-blocking activity[144]. This approach has been replicated in seasonal birch pollen allergy where a cocktail of three monoclonal antibodies directed against the major birch allergen Bet v 1 was effective in inhibiting the clinical response to birch pollen nasal challenge for at least 2 months[145].

A complementary approach involving selective induction of allergen-specific blocking antibodies with minimal T cell responses involves active immunization with recombinant allergen-derived B cell peptides. A mixture of recombinant non-IgE reactive linear peptides (BM32) derived from the grass pollen allergens *Phleum* p 1, 2, 5 and 6 were fused to a carrier protein (Pre-S protein, derived from hepatitis C virus)[125]. A placebo-controlled field study in 181 participants demonstrated increases in allergen-specific IgG1 and IgG4 and minimal changes in IgE responses after BM32 treatment. The primary analysis of seasonal combined symptom medication scores was encouraging but did not achieve significance, although asthma symptom scores and quality of life scores improved[125]. Results of phase 3 trials are awaited.

Allergen combination strategies. Combination strategies of allergen either plus TLR agonists or in combination with the recently available monoclonal antibodies targeting the T_H2 cell pathway provide new opportunities for improving efficacy and long-term tolerance. Targeting TLRs[146] such as TLR4 with selective agonists in combination with allergen, with the aim of favouring T_H1 cell responses over T_H2 cell responses, has been tested in a phase 3 trial. Four injections of the TLR4 agonist monophosphoryl lipid A combined with a grass pollen allergoid showed modest efficacy, with a 13% reduction in combined symptom–medication scores[76].

The combination of allergen with anti-IgE monoclonal antibody (omalizumab) as an adjunct or pretreatment with inhalant allergen immunotherapy reduced symptom scores and systemic IgE-mediated side effects but had no impact on long-term tolerance[147,148].

Grass pollen subcutaneous immunotherapy combined with an anti-IL-4 antibody downregulated circulating IL-4-expressing T_H2 cells in blood but had no effect on the magnitude or duration of suppression of allergen-induced late skin responses compared with allergen alone[149]. The combination of grass pollen allergen with an anti-IL-4 receptor (anti-IL-4R) antibody would target both IL-4-dependent

and IL-13-dependent pathways, and is currently being tested with both inhalant immunotherapy (NCT04502966)[150,151] and oral peanut immunotherapy (NCT03682770)[152].

The importance of innate immune responses involving the respiratory epithelium and distinct subsets of dendritic cells and ILCs that preferentially drive T_H2 cell responses is increasingly recognized[47]. Anti-OX40 in combination with allergen represents an alternative strategy to divert T_H2-type responses[153]. Combinations of allergen with antibodies against pro-allergic epithelial cytokines such as thymic stromal lymphopoietin (TSLP) (NCT02237196)[154] and IL-33 (REF.[155]) are currently under evaluation.

Perspectives

Currently, our best approach for achieving long-term tolerance for inhalant allergies is allergen immunotherapy with whole allergen extracts for 3 years[102]. This is based on proven long-term clinical efficacy paralleled by downregulation of allergen-specific T_H2 cell responses and durable increases in 'protective' antibody responses that persist long after discontinuation of treatment[21,23,93]. For the subcutaneous route, the IgE-inhibitory activity is predominantly IgG, whereas for sublingual immunotherapy IgA is the dominant isotype[105]. The fact that sublingual and subcutaneous immunotherapy involve distinct mechanisms implies that it may be possible to combine both treatments in resistant cases. Immunotherapy for asthma remains a substantial unmet need for which the sublingual route may be preferable on grounds of safety and proven effects of HDM sublingual tablets on reducing steroid burden[100] and preventing asthma exacerbations[101].

Advances in molecular allergology have provided recombinant allergens that facilitate more precision for allergy diagnosis and for the selection of patients for allergen immunotherapy[126]. At present, recombinant allergen immunotherapy has not added value in terms of efficacy or safety over currently available whole allergen extracts[122,123] but recombinant hypoallergenic variants may have such potential. In the future, immunotherapy could involve tailor-made vaccines containing major allergens or hypoallergenic variants, based on personalized profiles of IgE sensitivity[121]. Allergen modifications to preferentially target T cell responses and reduce IgE-dependent side effects have so far met with limited success[140], suggesting that targeting both T cell and B cell arms is important. However, passive immunotherapy with recombinant IgG4 antibodies or targeting B cells using active immunization with recombinant allergen peptides that favour preferential IgG antibody responses are proving to be safe and effective[125], with phase 3 trials now in progress. Given the key requirement for IgE-blocking antibodies for long-term clinical efficacy, future studies are needed to determine whether this requires ongoing affinity maturation of B cell IgG responses (that is, with more effective binding of individual epitopes) on prolonged exposure or increased avidity of blocking antibodies due to increased polyclonality (that is, recognition of more epitopes with more effective blockade of IgE cross-linking[156]).

Combination strategies provide new opportunities to improve efficacy and safety of conventional immunotherapy and achieve long-term tolerance with shorter more convenient courses. Based on the known mechanisms of immunotherapy, these 'allergen+' strategies include combinations with TLR agonists[76,131] or monoclonal antibodies targeting IgE[148] or the T_H2 cell pathway[150,151]. An attractive approach is the combination of allergen with antibodies directed 'upstream' at epithelial cytokines that regulate T_H2 cell pathways[154,155].

Long-term tolerance after oral immunotherapy for food allergies has proved elusive[53]. A recent breakthrough has been that very early intervention with peanut oral immunotherapy in young children less than 4 years old, when associated with low specific IgE levels and reduced basophil activation, may result in sustained unresponsiveness to oral peanut challenge for several months (IMPACT study)[60]. Pending safety studies, combination strategies in this age group that include either anti-TSLP or anti-IL-33 antibodies would seem logical to induce more durable tolerance[154,155]. Targeting dendritic cells directly with epicutaneous peanut immunotherapy has been shown to be safer, albeit less effective, than the oral route[118]. However, continued epicutaneous peanut immunotherapy may reduce the risk of anaphylaxis upon accidental exposure to trace amounts, which may be a more realistic goal, rather than attempting to achieve long-term tolerance via oral peanut immunotherapy with attendant risks of anaphylaxis due to the treatment[13].

As a result of the remarkable success and safety of early introduction of peanut as a primary preventive strategy[119,120], similar studies in infants who are at risk are ongoing for prevention of other food allergies including shrimp, cashew[157] and milk[158] allergy. It is therefore logical to consider primary preventive strategies against developing inhalant allergies. For example, preliminary data have shown that with sublingual HDM treatment in infants who are at risk, it may be possible to prevent allergic asthma developing later in childhood[108,109].

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