Therapeutic vaccines for allergic disease

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Allergic diseases are highly prevalent worldwide and affect all age groups, contributing to a high personal and socioeconomic burden. Treatment with an “allergy vaccine” or allergen immunotherapy aims to provide long-lasting benefits by inducing unresponsiveness to the relevant antigen. The consequences of the therapy are considered disease modifying and range from dampening of the immediate immune responses to the reduction of secondary tissue remodeling. Furthermore, allergen immunotherapy interventions have a potential to slow or cease the development of additional allergic manifestations with a long-term overall effect on morbidity and quality of life. Here, we review proposed mechanisms underlying the therapeutic effects of immunotherapy for allergic diseases. Further, we discuss both standard and novel approaches and possible future directions in the development of allergen immunotherapy.

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INTRODUCTION

Allergic diseases, such as atopic dermatitis (AD), allergic asthma (AA), allergic rhinitis (AR), and food allergy (FA) are highly prevalent worldwide. While multiple therapeutic approaches are available to treat the allergy symptoms, the “allergy vaccine” or “allergen-specific immunotherapy” (AIT; colloq. “allergy shot”) is currently the only option offering a disease-modifying intervention. The ultimate goal of the AIT protocol is to provide specific curative therapy with associated long-term tolerance. However, even a partial reduction in disease severity and medication use represent clinically relevant beneficial outcomes of therapy. Moreover, both a reduction in symptoms per se, and slowed progression of the “allergic march” (i.e., appearance of subsequent allergic manifestations in a given patient in time) as well as a decrease in induction of new sensitizations have a great impact on well-being and quality of life. Finally, resultant reduction in the use of classically administered medication, such as corticosteroids or antihistamines, leads to a decrease in the associated side effects, risks, and costs. As a consequence, there are already indicators that the AIT leads to a reduction of the public healthcare burden.

The history of AIT started over a century ago, when Leonard Noon reported the first successful attempt to prevent AR by inoculation of an allergic patient with pollen extract before the pollen season. Throughout those early experiments Noon was able to determine that the sensitivity threshold could be raised by a gradual increase of the dose over time. In 1954 Frankland and Austin conducted the first double-blinded placebo-controlled trial for treatment of AR and associated asthma, using crude pollen extract (pollaccine) and isolated protein component. Over a decade later, by following a cohort of asthmatic children, Johnstone and Dutton demonstrated the value of desensitisation in decreasing asthma persistence over time. Finally, a 10-year follow-up, the Preventive Allergy Treatment, study has proven that specific AIT has a potential to slow or cease the allergic march and the development of additional allergic manifestations.

MECHANISM OF IGE-MEDIATED ALLERGIC REACTIONS

Development of sensitization begins with penetration of antigen through a body barrier which is accompanied by release of epithelial alarmins and influx of early inflammatory cells. This is followed by T cell priming, initiated upon first antigen encounter by antigen presenting cells (APCs) serving this barrier (i.e., a “sensitization phase”). Activation of the immune system during recall responses requires subsequent antigen entry and is promoted by the activated allergen-specific effector memory T cells, antigen-specific IgE antibodies, tissue resident mast cells and basophils. Because of the greater magnitude of the secondary responses and fast time course of the IgE-mediated allergic reaction following the antigen recognition, these immediate consequences can be life-threatening in highly allergic patients.

Allergen encounter and the epithelial response

Exposure to an allergen through a body barrier (the skin, gut, nasal or respiratory epithelium or oral mucosa) starts a sequence of events critical to the character of the T cell response and additional secondary outcomes. It seems that enzymatic proteolytic activity of allergen components can actively increase the penetration and affect barrier quality by reducing cellular adhesion and induction of potentially barrier-disrupting mediators. Proteases are also involved in the itch sensation, one of the hallmarks of allergic reactions, independently of histamine via PAR-2 pathway, therefore perpetuating the itch-scratch cycle and associating with clinical deterioration.

Emerging new evidence suggests that antigen exposure via the skin route in the context of disrupted epidermal barrier particularly predisposes to the induction of allergy. This may
be partly explained by the pro-inflammatory role of the Major histocompatibility complex (MHC)-like molecule CD1a, which is highly expressed by Langerhans cells of the epidermis and by subsets of dermal dendritic cells. Allergen-derived phospholipase, present in insect and snake venoms as well as in other antigen sources such as house dust mite extract, generates antigenic lipids that are presented by CD1a to T cells further driving subsequent peptide-specific T cell and protein-specific IgE responses. This seems to be especially evident if there is already an underlying dysfunction with the integrity and function of the skin barrier, contained within the epidermis (such as resulting from a mutation in filaggrin or other "barrier genes") or if there is inflammation. Combined, the evolving data support the "dual allergen-exposure hypothesis", which predicts that the route of primary allergen exposure dictates the clinical outcome. Because of this additional, yet still relatively poorly understood complexity, for the purpose of this review we will specifically focus on the scenario where antigen encounter leads to a productive/activating response, resulting in allergic sensitization.

Penetration of an allergen itself or other accompanying components of the allergen extract, such as lipids, initiates a sequence of events in both the immune and non-immune components of the barrier (Fig. 1a). Specifically, activated allergen-exposed epithelia start releasing cytokines and alarmins, i.e., TSLP, IL-25, IL-33, as well as proinflammatory and chemotactic signals (cytokines: IL-1α, IL-6, IL-8, TNFα; chemokines: CCL-8 and CCL-20, CXCL-1-3). In addition, stimulated epithelia secrete a potent and multifunctional alarmin, high-mobility group box-1 (HMGB1) protein, which induces proliferation, differentiation, and recruitment of inflammatory cells and forms immunostimulatory complexes; HMGB1 can also enhance cytokine production resulting from TLR engagement. The protein was shown to be important in the pathogenesis of asthma and could potentially become a therapeutic target in AD, as demonstrated in a murine model.

Following alarmin release, immune cells accumulate locally, which results in the inflammation of the tissue. Interestingly, epithelial cytokines influence the Th2 predominance of the following response, which ultimately facilitates allergic sensitization. This is partly a result of the response of the tissue resident professional APCs (such as Langerhans cells or subsets of dendritic cell populations) to the epithelium-derived signals, leading to the adaptation of a Th2-promoting phenotype; this has a long-lasting impact on the direction of subsequent immune responses. In addition, innate lymphoid cells type 2 (ILC2s), which are potent secretors of IL-5, IL-4, and IL-13 are resident, and are also further recruited following stimulation by epithelial alarmins. Recently, ILC2s have been shown to be activated when interacting with aberrantly differentiated keratinocytes in vitro, due to a reduction in the KLRG-1-mediated inhibitory signaling they receive in this context and to keratinocyte overexpression of B7-H6, a ligand of NKp30. It has also been observed in murine asthma models that NK cells have a capability to prevent ILC recruitment after allergen stimulation. Development and recruitment of mast cells is also

Fig. 1 Antigen penetration through epithelial barrier and allergen sensitization
promoted by epithelial TSLP. In addition, observations following allergen extract application to respiratory epithelium show that neutrophils also accumulate early in the tissues, this early migration of neutrophils involves IL-8 and CXCL chemokines, which can be induced in epidermal keratinocytes. These release enzymes such as metalloproteases or elastases and reactive oxygen species contribute to the tissue damage and remodeling as well as mucin production. Furthermore, the accumulating granulocytes secrete serine proteases (cathepsin G and elastase), chymase and trypsin which have been shown to generate highly potent isoforms of IL-33 both in humans and murine models.

Sensitization phase
Following entry, allergens are taken up by the local APCs. Interestingly, besides their immunogenic role, enzymes contained within allergen extracts and venoms may also provide a source of in situ generated new antigens (neo-antigens), which can amplify subsequent adaptive immune responses, as described above. Specifically, phospholipase PLA2 has also been shown to be important source of generated new lipids for CD1-mediated antigen presentation, which are required by APCs to activate and their migration to local lymph nodes where these cells display the allergens on their surface, within the groove of antigen presenting molecules. The nature of the presentation (MHC class I, MHC class II, CD1a, CD1b, CD1c, CD1d, or MR1-mediated) is determined by the source and structure of the antigen itself, e.g., NK T cells have been shown to be required for early responses to environmental allergens in animal models. It is also of note that early NK T cell involvement may stretch beyond specific antigen recognition, since these cells have a capability to suppress protein-induced airway hyperreactivity and skin reactions in mice. Further, a combined lack of NK T and NK cells in the NK1.1 knock out animals results in inhibition of recruitment of eosinophils and T cells to the lungs as well as reduced Th2 and IL-12 production in situ in a model of AA. Interestingly, NK cells have also been shown to migrate to lymph nodes during the allergen sensitization phase; their role, however, is presently not clear.

Allergen presentation to the naïve T cells in the lymph nodes (Fig. b) results in the activation and clonal expansion of the antigen peptide-specific T cells, which recognize epitopes contained within the allergen. It seems that the vast majority of the expanding T cells are potent CD4+ cytokine secretors; this leads to profound changes in the local cytokine environment. Specifically, because the APCs were initially “primed” by the Th2-skewing inflammatory milieu, as described above, a Th2 phenotype bias is subsequently induced in the interacting T cells. However, a significant proportion of CD8+ allergen-specific T cells have also been shown in allergic patients and murine models. Following the antigen presentation and consequent clonal expansion within cytokine-rich domains of the lymph node, activated T cells lose the expression of lymphoid-tissue retaining chemokine receptors (e.g., CCR7) and migrate as effector memory cells to tissue sites (Fig. c), recruited by chemoattractants, and amplify tissue-resident T cell responses. The development of type 2 cytokine-producing allergen peptide-specific T cells promotes class-switching and the acquisition of allergen-specific IgE.

Secondary phase
A predominant effect following the secondary allergen encounter results from the CD4+ effector memory T cell function; these experienced cells of a largely type 2 phenotype actively release large amounts of cytokines (IL-4, IL-5, IL-13, IL-9) during recall responses to their cognate antigen. This is perpetuated by locally abundant and highly potent IL-33 isoforms, generated by neutrophil-derived proteases and other alarmins, which further recruit and stimulate cells to increase the expression of IL-4 and IL-13. While all these mechanisms lead to the evident type 2 predominance, additional T cell-secreted cytokines (i.e., IFNy, IL-22, IL-17A) are still relatively enriched and other Th subpopulations (Th1, Th17, Th22, Th9) have been also implicated during allergic inflammation. Finally, a direct cytotoxic effect, exerted on the epithelial cells, and attributed to CD8+ T cells, can be noted as a component of allergic responses. However, IFNy-dependent regulatory roles have also been proposed for this population in mice.

The specificity of the infiltrating T cells extends far beyond the recognition of peptides, as lipid-derived allergens can be recognized by CD1a-restricted and CD1d-restricted T cells. There is also a possibility that other unconventional T cell populations, such as those recognizing MR1 molecule-presented vitamin B derivatives, mucosal-associated T cells, or CD1b-restricted germline-encoded mycolyl-reactive T cells could enhance or mediate allergen-specific responses in some cases. Whether these populations can contribute to sensitization and/or response to allergens, however, remains to be formally proven. This resulting complex allergic milieu induces several downstream consequences, which ultimately compound the disease symptoms (Fig. 2). Specifically, further recruitment and activation of cell populations acting as effectors during the allergic inflammation (i.e., eosinophils, mast cells, basophils, neutrophils) by IL-3, IL-4, IL-5, GM-CSF, and TSLP is observed. Furthermore, induction of phenotypic and functional changes in monocytes and macrophages result in the generation of alternatively activated macrophages, which produce arginase-1 and contribute to tissue remodeling, angiogenesis, further Th2 bias of inflammatory responses or local immunosuppression. It has been also evidenced that the Th2 bias promotes survival of CD8+ T cells, further adding to the increase in the cellular infiltrate. Importantly, IL-4 and IL-13 induce further IgE class switch recombination in B cells, leading to the changes in the Ig profile in allergic patients, with IL-17A also recently identified as contributing to this effect. Abundantly secreted IgE antibodies bind to the high-affinity IgE receptor (FcεRI) on resident mast cells, eosinophils, and basophils. When the allergen crosslinks these membrane-bound IgE antibodies, cells rapidly degranulate, releasing inflammatory mediators, pre-synthesized and stored within cytoplasmic granules; activated cells also de novo synthesized mediators shortly after the stimulation. The mediators include histamine, multiple cytokines, leukotrienes, prostaglandins, and other lipid mediators such as platelet-activating factor. Their combined action results in the increase of vascular leak and immune cell extravasation, leading to the intensified cell influx into the site of inflammation as well as the appearance of the classical signs of inflammation, i.e., calor, dolor, rubor, tumor (heat, pain, redness, and swelling) in the affected tissue. In addition, release of enzymes, such as tryptase, serine proteases, and peroxidase or elastase, during the degranulation of effector cells contributes to the tissue damage. Furthermore, IgE also has an assisting role during antigen presentation, as it facilitates uptake of relevant antigen by mechanism involving both the high-affinity (FcεRI) and low-affinity (FcεRII) IgE receptors expressed by APCs in the skin (dermal dendritic cells and Langerhans cells) and B cells, respectively. This results in increased production of antigen-specific IgE, IgM, IgG1, and IgG2a, which promotes the induction of long-term adaptive memory. Finally, IgE antibodies seem to be also involved in the perpetuation of allergic inflammation in animal model of asthma in part through these mechanisms.

There are also many additional effects as a consequence of the Th2 inflammatory milieu, both in situ and in the distant organs,
including effects on epithelia in the lungs, gut, and skin. Cytokines and histamine induced during allergic inflammation affect the integrity and function of epithelial barriers, for example, by effects on tight junctions and cellular adhesion, as well as their impact on peptides, proteins, and enzymes critical to the maintenance of barrier integrity and function. The existence of a positive feedback loop between allergic and proinflammatory cytokines and epithelial alarmins which perpetuates the inflammation has also been proposed. This leads to compounded allergen penetration and sensitization as well as the increased propensity to infections. IL-4 and IL-13 stimulate goblet cells within the respiratory and gut epithelia to proliferate and produce mucus, while IL-13 and TNFα causes smooth muscle proliferation and hyperactivity.

**Fig. 2** Complexity of allergic milieu and its secondary outcomes

| Route of allergen introduction | Advancement (experimental/clinical phase) |
|-------------------------------|-----------------------------------------|
| Subcutaneous SCIT             | In clinic                                |
| Sublingual SLIT               | In clinic                                |
| Oral OIT                      | Phase 3 clinical trials, limited in clinic |
| Epicutaneous EPIT             | Phase 3 clinical trials                  |
| Intralymphatic ILIT           | Phase 3 clinical trials                  |
| Local nasal LNTIT             | Phase 1/2 clinical trials                |
| Intradermal IDIT              | Phase 2                                  |
| Intragastric IGIT             | Animal studies                           |

**ROUTES OF ALLERGEN INTRODUCTION AND CLINICAL AIT PROCEDURE**

Multiple allergen introduction routes are being utilized either clinically or experimentally (Table 1) with subcutaneous (SCIT) and sublingual (SLIT) AIT being best characterized and most commonly used for treatment. SCIT involves subcutaneous injection of the allergen-containing solution; SLIT is carried out with either a solution (Drop-SLIT) or tablets releasing allergen directly onto the oral mucosa. Furthermore, combination preparations, containing multiple allergens (e.g., grass pollen mix) are available for both SCIT and SLIT. SCIT and SLIT can differ in terms of efficacy, safety, and mechanism. Specifically, significant differences in the induction of allergen-specific antibodies can be seen, with SCIT inducing more IgG4 and more IgE blocking factor, and SLIT inducing higher transient IgE titers. The effect on facilitated antigen presentation inhibition also seems to be greater for SCIT, as is difference in basophil activation. Furthermore, while both antigen delivery routes result in significant IL-10 production, decreased IL-5 production has been observed uniquely in SCIT. These studies suggest differences in B and T cell responses, but additional mechanisms, such as involvement of mucosa-enriched...
CD1a-positive Langerhans cells within oral mucosa,\textsuperscript{102, 103} could shape immune responses locally. Similar differences could also potentially be implicated in differential responses to antigen delivery via novel routes, such as epicutaneous and nasal AIT. This difference could also result from specificity of allergen handling by Langerhans cells, which seem to be involved in maintenance of homeostasis in the skin\textsuperscript{104} and being enriched in nasal mucosa under allergen exposure.\textsuperscript{105} This lipid-restricted immune component is missing in the SCIT route, due to the low abundance in cells expressing high levels of CD1a below the dermis; the same will apply to the increasingly promising oral antigen delivery route.\textsuperscript{106–108} Due to the nature of AIT, the treatment is always focused on the confirmed allergens a patient reacts to. The basic AIT protocol involves introduction of that allergen in repeated and often escalating doses in a controlled setting (the “build-up phase”). This protocol may be modified depending on the severity of local or systemic reactions, and is followed by a longer-term “maintenance phase”. The completion of a full AIT schedule often allows for discontinuation of the therapy when satisfactory long-lasting tolerance is reached; however, depending on a patient, this may not be achieved during the immunotherapy course. These patients, however, still often benefit from an increase in the threshold of activation upon the allergen encounter. This state of partial tolerance mirrors a natural pattern of partial desensitization threshold of activation upon the allergen encounter. This state of anergy. Mainly CD4+Foxp3+ iTregs are induced, but also Foxp3+ regulatory iT1 and iT35 cells\textsuperscript{116, 120, 121} have been noted. The suppression can be observed at the level of the effector T cell proliferation\textsuperscript{130} and affects both CD4+ and CD8+ populations.\textsuperscript{131} Tregs exert those functions both directly and via their influence on the APCs.\textsuperscript{132} Specifically, secreted suppressing cytokines (IL-10, TGF\(_{\beta}\), and IL-35), which affect responses at multiple levels, provide potent immunosuppression mechanisms in both adaptive and innate immunity.\textsuperscript{133, 134} For example, these cytokines down-regulate antigen presenting molecules on APCs, thus affecting their ability to stimulate T cells, halting proliferation and promoting a regulatory phenotype. The effect can be observed at both the level of naive T cell priming as well as the recall responses.\textsuperscript{130} AIT has been demonstrated to result in Th subset redirection into Th1 cells,\textsuperscript{135–139} induction of anergic Th2 cells,\textsuperscript{140} and preferential deletion of the pathogenic T cell clones.\textsuperscript{141} In addition, Treg-derived IL-10 has the ability to downregulate the expression of proinflammatory cytokines secreted by the APCs.\textsuperscript{143} IL-10 is also thought to contribute to B cell class switching to IgG4 which has an IgE-blocking function. Acting directly in a contact-dependent fashion, Tregs also modulate function of these cells by engaging CD80/CD86 and providing inhibitory CTLA-4-mediated signals. Tregs can also compete with pathological effector T cells physically (simply by blocking their access to the DCs),\textsuperscript{144} reducing available IL-2\textsuperscript{145, 146} and stimulating tryptophan degradation by dendritic cell IDO (indoleamine-pyrrole 2,3-dioxygenase)\textsuperscript{147–149} which leads to metabolic disruption. Tregs facilitate cAMP-mediated effector T cell inhibition,\textsuperscript{146, 149, 150, 151} and can engage in adenosine-receptor immunosuppression\textsuperscript{152, 153} and contribute to the direct killing of antigen-specific effector T cells in a granzyme B and perforin-mediated fashion.\textsuperscript{154} Tregs have also been shown to prevent recruitment of mast cell progenitors in a murine model of asthma.\textsuperscript{155} In addition, induction of Tregs may promote beneficial allergy-allowing changes in further cell populations; it has been previously shown that Tregs have a direct suppressive effect on monocytes/macrophages\textsuperscript{156–158} mast cells,\textsuperscript{159, 160} and eosinophils.\textsuperscript{161}

The second regulatory cell type, which appears to have a beneficial role during AIT is a population of much less studied regulatory B cells (Breg).\textsuperscript{162, 163} These cells similarly secrete IL-10, TGF\(_{\beta}\), and IL-35, therefore being Treg counterparts homologous in their ability to affect immune responses. It seems that the IL-10-producing Breg subtype (B1r) increases during AIT.\textsuperscript{164} Allergen-specific Breg immunosuppressive capacity during AIT has been attributed to the production of IgG4 by these cells and the suppression of allergen-specific effector T cells.\textsuperscript{165} as well as the induction of Tregs by promoting conversion of CD4+CD25+ T cells into CD4+CD25- Treg cells.\textsuperscript{166} AIT leads to a complete or partial reversal of the consequences driven by effector T cell activation (Fig. 3); qualitative and quantitative changes in the inflammatory milieu result in beneficial secondary outcomes. Specifically, a decrease in class switching by B cells and a reduction of IgE production with an evident increase in IgA, IgG4, and IgG1 levels can be observed\textsuperscript{167}; these antibodies compete for allergen therefore increasing the threshold required for mast cell and basophil degranulation, IgE-mediated antigen uptake and development of memory IgE production.\textsuperscript{168} An increase in the blocking IgG antibodies can be assessed by a traditional functional test with patient serum (referred to as a “patient self-test” or “P-S test”) and other means.\textsuperscript{166–169} This is critical, as these latter antibodies compete with Fc\(_{\gamma}\)R1-immobilized IgE antibodies for allergen binding. Specifically, stabilization of the cells capable of degranulation by reducing the chance of IgE cross-linking and increasing activation threshold reduces risk of type I hypersensitivity reactions and IgE-mediated antigen presentation by the APCs. AIT also leads to the alleviation of inflammation by reduced local accumulation of basophils and eosinophils,\textsuperscript{170} with a similar effect on the reactivity and recruitment of neutrophils having also been demonstrated.\textsuperscript{171, 172} These result in a reduction in inflammation in the...
affected tissue, as shown both in double-blinded patient studies and animal models. Finally, AIT has also been shown to prevent ILC2 increase during pollen seasons in patients with AR by as yet unknown mechanisms.

**NOVEL APPROACHES AND FUTURE DIRECTIONS**

While a tremendous progress has been seen in the AIT field over the last decades, there is still a need for methods that increase convenience and patient safety as well as a spectrum of available AIT allergens. Novel approaches include the identification of new allergen delivery routes and novel antigen preparations as well as combination protocols, where AIT is carried out parallel to other treatments. Currently investigated novel AIT routes include oral (OIT), epicutaneous (EPIT), local nasal (LNIT), intralymphatic (ILIT), and intradermal (IDIT). To date, the intragastric (IGIT) route has only been tested in mice. While native allergen source or crude allergen extracts have been used in AIT protocols, these natural products may vary greatly in terms of allergen content. Recombinant allergens have an advantage of a standardized and well-defined manufacturing process, leading to product consistency and easy scalable production. However, individual antigens may not fully modulate the clinical response to the whole allergen source and side effects can be observed at a level similar to crude extracts. Furthermore, recombinant allergens pose a risk of inducing IgE production, which limits their use. Therefore, great effort is being made currently to improve allergen sources for AIT. Approaches to formulate these new allergen preparations focus on the use of specific proteins or allergen extract fractions or modified/engineered allergens, aiming to reduce IgE reactivity while retaining efficacy; these are investigated predominantly in classical SLIT/SCIT studies. Methods include the use of synthetic overlapping peptide epitopes, fusion proteins, or allergens that have been chemically modified, e.g., denatured (also known as “allergoids”). Also, modified or fragmented recombinant allergens, hypoallergenic recombinant allergen derivatives and allergen-derived peptides are being investigated currently. While all these T-cell directed approaches are protein/peptide-based, it is also conceivable that we will observe new AIT approaches, constructed around targeting of lipid-specific innate and adaptive immune responses in the future. Furthermore, innovative B-cell-focused approaches, aiming to induce responses promoting the generation of the IgG antibodies to compete with IgE for allergen binding are also being studied.

In addition, AIT preparations of allergens are being combined with a choice of specific carriers or adjuvants, for example, Toll-like receptor ligands or virus particles in combination with allergen preparations, to redirect immune response and induce a more favorable Th bias. Finally, introducing combinations of drugs and AIT, e.g., parallel use of AIT and treatment with additional biologics (e.g., anti-IgE antibody) or even defined bacterial strains in order to modulate the impact of the accompanying microbiome is also a potential...
new approach to develop safe and efficacious immunotherapy protocols.

SUMMARY

Multiple mechanisms are involved in the induction of antigen sensitization and subsequent allergic reactivity, both from the side of the immune system and the epithelial component of body barriers, which are the sites of allergen entry. AIT currently provides the only cause-directed treatment option for allergy sufferers, and aims to induce peripheral tolerance to the relevant antigen. As such, AIT has been shown to be efficacious and to have a direct effect on patient welfare and socioeconomic burden.

While AIT targets multiple allergic pathways, both the short-term and long-term beneficial outcomes involve the induction of allergen-specific regulatory T and B cells, directly and indirectly suppressing innate and adaptive effector populations. Consequently, additional beneficial outcomes result from the therapy, due to a reduction in chronic inflammation and tissue remodeling, inhibition of new sensitizations and slower progression of the “allergic march”. Novel AIT approaches include allergen modifications, altered formulations, and optimization of the vaccine introduction route to achieve tolerance induction and associated clinical benefit.

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AUTHOR CONTRIBUTIONS

D.G.O. and G.S.O. wrote the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

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