# The Use of Adjuvants for Enhancing Allergen Immunotherapy Efficacy

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**KEYWORDS**

• Allergen-specific immunotherapy • Immune tolerance • Adjuvants

**KEY POINTS**

- Allergen-specific immunotherapy currently represents the only curative treatment for allergy, but its broader application requires safer and more efficacious treatment protocols.
- Adjuvants can improve the efficacy of allergen-specific immunotherapy, and a variety of promising immunomodulatory adjuvants are currently being developed.
- Innovative strategies have been proposed to simplify immunization and to achieve long-term tolerance.

## INTRODUCTION

Allergic diseases are characterized by the seasonally recurring production of T helper 2 ($T_H2$) cytokines (eg, Interleukin [IL]-4, IL-5, and IL-13), which drive the production of allergen-specific type-E immunoglobulin (IgE) by B cells and the recruitment and sensitization of effector cells such as eosinophils, basophils, and mast cells.[1] Long-time surviving specific memory T cells and B cells generate a pool of cells that quickly expand upon rechallenge thereby forming an immunologic memory that allows quick responses against pathogens but unfortunately also seasonal recurrence of allergic symptoms. A key factor in the early-phase symptoms is that allergen-specific IgE binds to the high affinity IgE receptor, FcεR1, on the surface of mast cells, basophils,

Disclosure Statement: The author is consulting companies involved in the generation of vaccines (PLS-Design, LETI Pharma) and its institution receives grant support (PLS-Design, Allergopharma). The author is holding shares from PLS Design and is co-authoring patents on the use of immunomodulators for specific immunotherapy.

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Immunol Allergy Clin N Am 36 (2016) 125–145
http://dx.doi.org/10.1016/j.iac.2015.08.009 immunology.theclinics.com
0889-8561/16/$ – see front matter 

eosinophils, and dendritic cells (DCs) resulting in the rapid release of proinflammatory mediators such as histamine, prostaglandins, and leukotrienes, which elicit allergic symptoms such as itching, swelling and bronchoconstriction.[1] Late-phase reactions are mediated by infiltrating T cells that release $T_H2$ cytokines triggering additional tissue inflammation.

Allergen-specific immunotherapy (SIT) is currently the only curative treatment able to change the seasonal recurring natural course of IgE-mediated allergies and to induce long-term remission.[2] By exposing allergic patients to increasing doses of allergen, this therapeutic strategy aims to re-educate the immune system to promote a tolerogenic response toward a specific allergen.[3] This tolerogenic response is thought to be mediated by a change in immunologic memory. Effective immunotherapy is associated with the induction of distinct subsets of regulatory T cells (Tregs) that induce peripheral tolerance by increased secretion of IL-10 and transforming growth factor (TGF)-β, which increase the production of IgG4 and IgA antibodies.[4] In clinical settings, successful SIT is defined by a marked reduction in symptom duration and severity at the time of allergen exposure, a decrease in the use of antiallergic drugs, and an overall improvement in the quality of life of affected patients.[1]

However, despite great progress in the last decade, SIT faces several problems regarding its efficacy, side effects, low patient adherence, and the high cost owing to the long duration (3–5 years) of treatment.[5] It is estimated that less than 5% of all allergic patients, who could potentially benefit from allergy immunotherapy, actually undergo this treatment. Thus, finding new strategies to enhance SIT safety, more compact treatment regimens, and improved efficacy represents major objectives of current research efforts, which will be instrumental for improving a broader implementation of SIT in the clinic.

Factors that influence the safety and efficacy of SIT include the pattern of sensitization, the nature of the allergen preparation (allergen extracts, adjuvants, and conjugated molecules), and the route of administration (subcutaneous or sublingual). Thus, the optimization of allergen/adjuvant formulations and their mode of administration is currently a bottle neck in specific immunotherapy.[6] Subcutaneous immunotherapy (SCIT) is the most commonly used form of SIT and is found to be effective in adults and children suffering from allergies to house dust mites, animal dander, and pollen.[7] However SCIT requires frequent injections and can be associated with allergic side effects, including fatal airway obstruction and anaphylaxis. Other alternative methods of delivery such as epicutaneous, intralymphatic, oral, or sublingual immunotherapies have been proposed and are currently being evaluated.[8] Because of its noninvasive character and good efficacy, sublingual immunotherapy is now considered a promising alternative to SCIT for respiratory allergies to grass and tree pollen or house dust mite allergens.[9]

In recent years, considerable research effort has been put into the chemical modification of allergens to improve the efficacy and safety of SIT, but also the demand of drug authorities to standardize allergen preparations has consolidated the available allergen preparations. Various strategies have been developed to modify allergenic molecules into safer hypoallergenic derivatives to limit adverse IgE-mediated reactions while maintaining their immunogenic properties.[10–13] Current research shows that allergenic peptides and various forms of recombinant allergens (hypoallergens, dimers, trimers, fusion proteins) can be efficient in controlling allergic inflammation and inhibiting symptoms of asthma notably by inducing the production of inhibitory antibodies.[12,14,15]

The use of appropriate immunomodulatory adjuvants is a particularly promising strategy to improve the safety and efficacy of current SIT protocols, because a