Vaccine development for allergen-specific immunotherapy based on recombinant allergens and synthetic allergen peptides: Lessons from the past and novel mechanisms of action for the future

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In the past, the development of more effective, safe, convenient, broadly applicable, and easy to manufacture vaccines for allergen-specific immunotherapy (AIT) has been limited by the poor quality of natural allergen extracts. Progress made in the field of molecular allergen characterization has now made it possible to produce defined vaccines for AIT and eventually for preventive allergy vaccination based on recombinant DNA technology and synthetic peptide chemistry. Here we review the characteristics of recombinant and synthetic allergy vaccines that have reached clinical evaluation and discuss how molecular vaccine approaches can make AIT more safe and effective and thus more convenient. Furthermore, we discuss how new technologies can facilitate the reproducible manufacturing of vaccines of pharmaceutical grade for inhalant, food, and venom allergens. Allergy vaccines in clinical trials based on recombinant allergens, recombinant allergen derivatives, and synthetic peptides allow us to target selectively different immune mechanisms, and certain of those show features that might make them applicable not only for therapeutic but also for prophylactic vaccination. (J Allergy Clin Immunol 2016;137:351-7.)

Key words: *Allergy, allergen, allergen-specific immunotherapy, allergy vaccine, preventive allergy vaccine*

Abbreviation used
AIT: Allergen-specific immunotherapy

Allergen-specific immunotherapy (AIT) was reported first by Leonard Noon in 1911.[1] Noon injected grass pollen extract into allergic patients and, despite the occurrence of side effects, observed clinical improvement for almost 1 year in the treated patients. In his article Noon quotes earlier work by William Dunbar,[2] who had shown that anti-sera raised against pollen allergen extract could neutralize allergen-induced conjunctival inflammation. The early work of Dunbar had already indicated that a major effect of AIT was caused by induction of allergen-specific blocking antibodies. In 1935, more than 40 years before the identification of IgE antibodies, Cooke et al[3] reported a series of elegant experiments showing that allergen-specific IgG antibodies induced by AIT can suppress allergen-induced skin inflammation. Since then, the importance of allergen-specific IgG antibodies that compete with IgE for binding to the allergens has been demonstrated by numerous studies as a major mechanism of the mode of action of AIT,[4] and therefore one might consider AIT and in particular the traditional form of subcutaneous AIT as a therapeutic vaccine.[5]

There are several important features that suggest that AIT has many advantages over symptomatic treatment with anti-inflammatory drugs and biologics when applied as recommended according to guidelines.[6] First of all, AIT functions in an allergen-specific and thus causative manner as a therapeutic vaccine. It uses the immune system of the patient to establish a counterimmune response, antagonizing the allergic immune response by vaccination with the disease-causing allergens or derivatives thereof. Therefore, as with other vaccines, allergy vaccines can be relatively easily produced, and the costs of AIT are low, in particular when compared with those of treatment with biologic agents, such as anti-cytokine antibodies.[7] Unlike anti-inflammatory treatment, AIT can stop the progression of mild forms (ie, rhinitis) of allergy toward severe forms (ie, asthma) and thus modifies the natural course of disease.[8,9] Furthermore, AIT has long-lasting effects, even after discontinuation of treatment, which cannot be achieved with symptomatic treatment.[10] The achievement of long-term "clinical tolerance" can be achieved through induction of long-lived B cells or plasma cells secreting high-affinity antibodies[11] and/or through a reduction in boosts of allergen-specific IgE, which occurs after natural allergen contact.[12-14]

Diagnosis of the disease-causing allergens and monitoring of treatment have been greatly facilitated through the availability of molecular allergy diagnosis, also termed component-resolved

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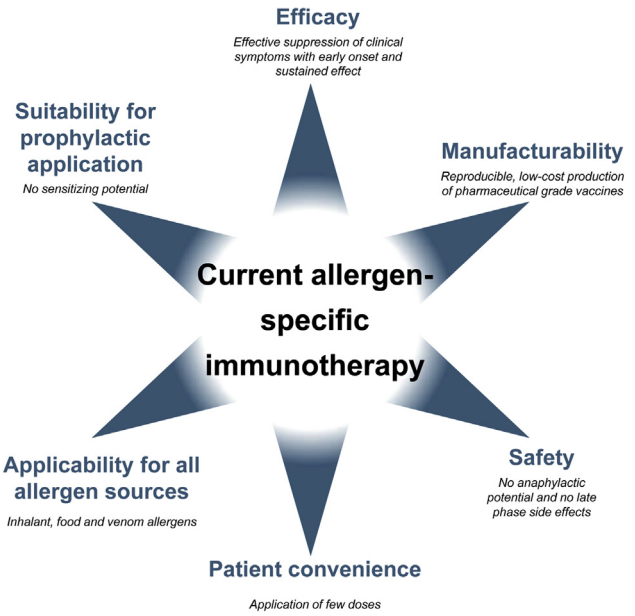

FIG 1. Requirements for improved allergy vaccines.

allergy diagnosis.[15-18] For example, microarrayed allergen molecules allow detection of IgE reactivities and treatment-induced IgG antibody responses toward a comprehensive set of allergens.[16] Thus tools are available for more precise prescription of allergy vaccines and for controlling the effects of the vaccine.[16,19]

However, there are several important bottlenecks (Fig 1) that limit the broad applicability of AIT for allergy treatment. In this review we will discuss how these bottlenecks have been addressed in the past with traditional technologies and how modern technologies of molecular treatment might lead to a breakthrough of AIT not only for global allergy treatment but also ultimately for allergy prevention.

AREAS OF AIT THAT NEED IMPROVEMENT

Fig 1 provides an overview of areas in which improvement of AIT is needed. Some of these areas (safety, efficacy, and convenience) are closely connected to each other. A major problem in AIT is that administration of allergens can induce side effects in patients, which, in the worst-case scenario, can lead to anaphylactic shock and death.[20] Side effects can be classified as immediate side effects, which are caused by allergen-induced cross-linking of mast cell– and basophil-bound IgE antibodies. These side effects occur within 30 minutes after administration of the vaccine and, when induced systemically, can give rise to life-threatening anaphylactic shock. Systemic activation of mast cells and basophils occurs mainly when relevant doses of IgE-reactive allergens are distributed systemically in the body.

A reduction in the risk of immediate systemic side effects can be achieved by keeping allergens locally bound at the application site, such as through the use of certain adjuvants, such as aluminum hydroxide, which has been introduced already in 1935 and led to a profound reduction of severe systemic side effects (Fig 2).[21] Another way to reduce side effects has been reduction of the IgE reactivity of allergen extracts, which in the past has been achieved by chemical modification, such as denaturation with aldehydes.[22] Such modified allergen extracts that

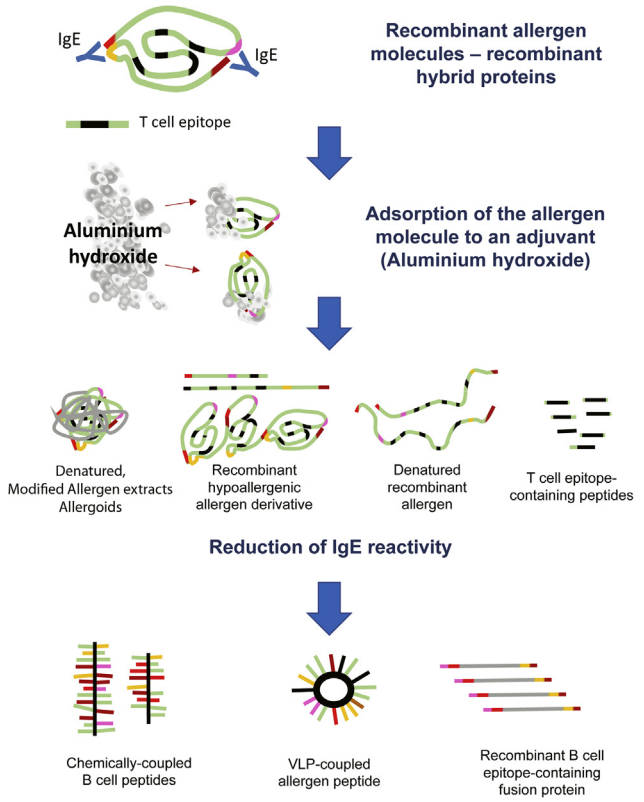

FIG 2. Steps toward improvement of allergy vaccines.

exhibit reduced IgE reactivity are termed "allergoids" (Fig 2). Interestingly, even strong reduction of IgE reactivity cannot eliminate side effects because late-phase side effects can occur even in the absence of IgE reactivity caused by the presence of undestroyed T-cell epitopes. In a classical study it has been shown that even non–IgE-reactive T-cell epitope–containing allergen peptides can induce systemic late-phase side effects that occur after hours and are caused by IgE-independent activation of allergen-specific T cells.[23] Late-phase side effects have been also reported for AIT with allergoids made from natural allergen extracts.[24,25] Because the IgE reactivity of allergoids is usually strongly reduced, these late-phase side effects can be also mediated by activation of allergen-specific T cells because allergoids retain their ability to stimulate T cells.[26]

Another possibility to reduce the risk of side effects is to begin treatment with very low doses and to continuously increase the dose until a therapeutically effective maintenance dose has been reached. As a result of the need for updosing, AIT requires multiple administrations, which make the treatment inconvenient. Therefore alternative routes of administration, such as sublingual, oral, and epicutaneous application, were developed, but these treatments also require frequent administration and are inconvenient.[27-30] For example, sublingual treatment requires daily administration, and therefore it is not surprising that the compliance of patients receiving AIT is low and particularly low for sublingual AIT.[31]

Another area of AIT in which improvement is needed is clinical efficacy. Very often it is not possible to reach and maintain the therapeutically active dose in patients because of side effects.