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Allergy vaccines: dreams and reality

Reto Crameri

Allergy, extrinsic asthma and atopic eczema derive from deregulated immune responses against innocuous antigens. The incidence of atopic diseases is actually affecting approximately 30% of the population in industrialized countries. Although much progress has been achieved in the development of efficient symptomatic treatments for allergic diseases, the only curative treatment remains allergen-specific immunotherapy. In contrast to classical vaccines, which elicit strong host immune responses after one or a few injections, allergen-specific immunotherapy might require a long treatment time of 3–5 years with up to 80 injections to confer some protection. The reality is that 'allergy vaccines' achieve beneficial effects through immunomodulation, which takes a long time to establish. The dream would be to develop highly efficient allergy vaccines able to cure the disease with a few injections.

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Historical background

The term 'allergy' is derived from the Greek words allos (other) and ergon (work, action) and was first used by the Viennese pediatrician von Pirquet to describe a changed or altered reactivity of the immune system [1]. The first documented clinical report of an allergy goes back to Bostock, who described catarrhus aestivus or hay fever in 1819 [2]. In 1873, Blackley identified pollen grains as the major causative agents of hay fever in a self-experiment [3]. First desensitization experiments were already conducted with grass pollen extracts in 1911 and can be considered as the start of allergen-specific immunotherapy (SIT) [4]. The discovery of a transferable tissue-sensitizing factor in the serum by Prausnitz and Küster [5], and the biochemical identification of this factor as a new immunoglobulin subclass (IgE) by Johansson and Bennich, and Ishizaka and Ishizaka in 1967 [6,7], opened the area of modern allergology.

Pathophysiology & epidemiology of allergic diseases

The common hallmark of allergic diseases is the production of allergen-specific IgE raised against normally innocuous environmental allergens. In sensitized (atopic) individuals, allergen exposure induces crosslinking of high-affinity FcεRI receptor-bound IgE of effector cells. Upon receptor aggregation, intracellular domains of the β- and γ-chain of FcεRI are phosphorylated by receptor-associated protein tyrosine kinases and, hence, link the receptor to signal-transduction pathways [8]. Intracellular signals finally result in the immediate release of histamine [9], cysteinyl-leukotrienes LTC4, LTD4, LTE4 and prostaglandin D2, which trigger inflammation and allergy responses [10].

Allergic diseases can be roughly subdivided in three groups according to their physical locations; examples include allergic rhinitis, allergic asthma and atopic eczema, earlier termed atopic dermatitis [11]. All three disease groups are related to the production of allergen-specific IgE after exposure to environmental allergens and the reasons why exposure causes atopic disorders in some individuals but not others is still not fully understood. It is, however, clear that strong interactions between environmental and genetic factors are involved in the development of atopy [12]. The incidence of allergic diseases has increased continuously during the

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last decades. The most recent surveys indicate that approximately 50% of the population in western countries is sensitized against allergens, whereas up to 30% develop allergic symptoms. Although SIT is the only treatment able to cure allergic diseases, only a minority of the allergy patients choose SIT as a therapy [101], mainly because it involves 30–80 doctor visits over a period of 3–5 years and also partly because of the lack of clinics specialized in the treatment of allergy and to an insufficient number of allergologists [102]. Therefore, every treatment schedule able to shorten the treatment period would strongly contribute to increase the patient's compliance and, as a consequence thereof, the market size for SIT that, at present, has an estimated global small volume of approximately US$500 million/year.

Current understanding of the mechanisms of SIT

Despite being used successfully in clinical practice since the beginning of the last century, the mechanisms underlying successful immunotherapy are still incompletely defined, mainly because of the use of poorly characterized allergen extracts, differences in treatment protocols and in the end points used to define SIT efficacy [8]. It is clear that allergens, as with any other antigen, must reach the organized lymphoid tissue in order to elicit an immune response [13]. Allergens are taken up by antigen-presenting cells (APCs) in the periphery through mucosal surfaces of the upper and lower respiratory and intestinal tracts, or through the skin. If an antigen does not reach secondary lymphoid organs in minimum dose or for sufficiently long time periods, it is ignored by immune cells, while antigens reaching and persisting in the lymph nodes in excessive amounts for long time periods delete primed T cells to avoid exaggerated immune responses [13]. Following recognition and uptake of the allergen, mature dendritic cells migrate to the T-cell-rich area of draining lymph nodes, display an array of allergen-derived peptides on the surface of MHC molecules and acquire the cellular specialization to select and activate naive T cells. By the nature of the signals they provide to naive T cells, APCs are critical for polarizing T helper (Th)0 helper cells into either Th1 cells, secreting predominantly INF-γ and IL-2, or Th2 cells, secreting predominantly IL-4, IL-5 and IL-13 [14], and for inducing long-lived memory Th cells. The current view is that, under the influence of IL-4, naive T cells activated by allergen-derived peptides presented in the MHC class II context differentiate into Th2 cells. Th2 effector cells produce mainly IL-4, IL-5 and IL-13 and mediate several regulatory and effectors functions. The Th2 cytokines induce the switch to, and production of, allergen-specific IgE by B cells, development and recruitment of eosinophils, production of mucus and contraction of smooth muscles ending in clinical symptoms associated with allergy [14,15]. It is suggested that distinct T-cell subpopulations discriminated on the basis of cytokine secretion and function counterregulate each other and play a decisive role for antigen responsiveness and tolerance [16]. However, a further subtype of T cells, termed regulatory T cells (Treg) has been shown to be able to inhibit the development of allergic Th2-mediated responses [17,18] and play a major role in SIT [19]. Tr1 cells [18] produce high levels of IL-10, low levels of IL-2 but no IL-4, suppress the proliferation of $CD4^+$ T-cells in response to antigen and actively downregulate a pathological immune response *in vivo*. As Treg cells are a major source of IL-10, it has been postulated that Treg cells secreting IL-10 are involved in the suppression of allergic Th2 responses in humans. The production of increased IL-10 levels in successful SIT studies support this hypothesis [19–21]. There is strong evidence that peripheral T-cell regulation has a crucial role in the control of harmful T-cell responses [22,23] and that Tr1 cells consistently represent the predominant T-cell subset controlling immune responses to allergens in healthy individuals. As the peripheral T-cell repertoire of allergic patients and healthy individuals recognize the same T-cell epitopes of an allergen [24], it is assumed that the balance between allergen-specific Tr1 and Th2 cells is decisive for the development of a healthy or allergic immune response to allergens [25]. Naive peripheral T cells are able to acquire regulatory functions as a consequence of peripheral induction after exposure to antigen [26]. These cells, termed natural or adaptive Treg, are characterized by the expression of the anti-inflammatory cytokines IL-10 (Tr1) [25] and/or TGFβ (Th3) [27]. Although a reduction in the numbers of mast cells and eosinophils, including the release of mediators, is associated with successful allergen SIT [28], the induction of a tolerant state in peripheral T cells appears to represent an essential step to achieve protection against environmental allergens [29].

Current immunotherapeutic treatment of allergic diseases

In spite of the fast progress in understanding the mechanisms underlying a successful SIT, clinical progress in the treatment of allergic diseases has been moderate. The majority of patients are basically treated the same as patients were treated almost a century ago [30], with some modifications related to the addition of adjuvants, or chemical modification of allergens, aimed to reach a depot effect and to improve efficacy and safety of the therapy. Subcutaneous immunotherapy (SCIT) consists of the administration of increasing doses of allergen extract to which the patient is allergic. Typically, a dose-escalation phase is initially employed and is followed by a maintenance phase of monthly injections lasting several years. More recently, sublingual immunotheraphy (SLIT) has been validated as a new route of allergen administration [31,32]. Although mucosal routes of administration are still subject of controversial debates [33,34], SLIT is used increasingly as a therapeutic intervention, especially in Europe [32]. However, one of the biggest issues in both SCIT and SLIT is the lack of uniformly standardized vaccines, since every manufacturer uses in-house-developed standardization methods. In Europe, current regulations recommend that each manufacturer produces an in-house reference preparation and use it for batch-to-batch control using scientifically based laboratory testing [35]. The significance of the major allergen content of allergy vaccines was recognized and is now established

in the WHO recommendations [36] and the European pharmacopoeia [37]. In the USA, the regulation of allergen extracts differs essentially from that of Europe. The US FDA issues common standards and assays mandatory for all manufacturers [38]. However, in daily clinical practice, most SIT vaccines in the USA are formulated using aqueous extracts without depot adjuvants and many of the vaccines are made up in the physician's office under uncontrolled conditions, in contrast to European practice where the vaccines used are commercial products. The purpose of standardization is to minimize the qualitative and quantitative variation in the composition of the final products to obtain higher levels of safety, efficacy and accuracy in allergy diagnosis and allergy vaccination; however, we are far from the optimum, as demonstrated, for example, by the huge differences in the content of major allergens in different commercial extracts ranging over three orders of magnitude [39].

A second problem for the comparison of the efficacy of SIT is that the methods and experimental designs used in clinical trials are quite heterogeneous and no unambiguously accepted methodological standards are available [40]. This unsatisfactory situation does not allow a comparison of the efficacy obtained in different clinical trials and, as a consequence thereof, unequivocal confirmation of the clinical value of SIT as an effective treatment to reduce disease severity.

Current clinical developments in SIT

The most important current developments in SIT are summarized in TABLE 1. The perhaps more advanced approach relies on using recombinant allergens to improve safety and efficacy of SIT [41]. The primary sequences of the most important allergens from mites, pollens, insects, animal dander, fungi and foods have been derived from cloning programs and are deposited in public databases [103,104]. Starting from the known sequences, these allergens can be produced as highly pure, perfectly standardized, recombinant protein preparations satisfying the requirement for therapeutic applications.

The first immunotherapy trial with a recombinant allergen has been performed with genetically modified hypoallergenic derivatives of the major birch pollen allergen Bet v 1 [42]. The multicenter, randomized, double-blind, placebo-controlled study enrolled 124 patients with birch pollen allergy. Patients were allocated to three treatment groups: placebo (n = 27), Bet v 1 fragments (n = 18) and Bet v 1 trimer (n = 21). They received eight subcutaneous injections containing increasing doses (1 to 80 µg) of verum absorbed to aluminium hydroxide or placebo in 1- to 2-weekly intervals as preseasonal treatment. Patients developed robust IgG antibody responses against natural Bet v 1, which showed cross-reactivity to Bet v 1-related pollen allergens from other trees and from food [42,43]. Investigations of cytokine responses conducted in one of the study centers showed that treatment with the trimer resulted in a significant reduction in IL-5- and IL-13-producing cells when compared pre- and post-treatment, which is indicative of a suppression of Th2 responses [44]. The results from measurements of immunologic parameters provide an encouraging basis for further developments of hypoallergenic variants, but emphasis must be placed on the generation of data to provide evidence of clinical efficacy because this study reports only a trend toward clinical improvement.

A second study was performed with a folding variant of rBet v 1 (rBet v1-FV [45]) adsorbed to aluminium hydroxide. Subjects with birch pollen rhinitis were included in an open, randomized, comparative study of recombinant Bet v 1-FV and a natural birch pollen extract [46]. Treatment was administered over a period of 4 months before the birch pollen season, with injections administered at weekly intervals. The maximum dose of Bet v 1-FV was 80 µg, approximately fourfold higher than the Bet v 1 content of the natural extract used in the comparative group of patients. Preliminary results following the first year's treatment indicate that the symptom-medication score for subjects receiving Bet v 1-FV is favorably less that that for subjects receiving the natural pollen extract, and the scores for

Table 1. Current developments in allergen-specific immunotherapy.

Development direction	Advantages	Disadvantages	Ref.
Vaccines			
Recombinant allergens	Producible as standardized drugs	Development costs	[47,48,59]
Hypoallergens	Lack of side effects, standardized molecules	Development costs	[42–44,46,59]
Peptide-based SIT	Lack of side effects, standardized molecules	Patient specificity, multicomponent vaccines	[20,53–56,85]
Adjuvants			
Immunostimulatory adjuvants	Increased immune responses	Mode of action and side effects largely unknown	[52,84,86]
Application routes			
Sublingual immunotherapy	Compliance, reduced side effects	Clinical efficacy still controversial	[31–34,87]
Intralymphatic immunotherapy	Reduced treatment time, compliance	Clinical efficacy not yet established	[68]

SIT: Allergen-specific immunotherapy.

both groups are superior to those of a reference group treated with antisymptomatic drugs that served as an additional control. As for the former study, results are encouraging, but final data on clinical efficacy will be important for an objective judgment of the potential of hypoallergenic variants as allergy vaccines.

The first results from the largest trial performed with wild-type recombinant Bet v 1 were presented at the 25th European Academy of Allergology and Clinical Immunology (EAACI) symposium in Vienna, 2006 [47]. In a multicenter, randomized, double-blind, placebo-controlled trial, 147 patients with allergic rhinoconjunctivitis to birch pollen were randomized in four groups to receive either a standard therapy with birch pollen extract, a recombinant Bet v 1, a naturally purified Bet v 1 preparation or a placebo therapy. Patients received aluminium hydroxide-adsorbed preparations in a preseasonal build-up phase and monthly injections with a maximal maintenance dose of Bet v 1 15 µg for 2 consecutive years after baseline treatment. Clinical efficacy was assessed in 125 patients during the first pollen season and in 116 patients during the second pollen season. During the first pollen season, the symptom scores were significantly reduced in the three actively treated groups compared with the placebo group, paralleled by a significant reduction of the medication scores. Similar results were observed during the second season in the three active groups, and symptoms and medication scores between the natural Bet v 1, recombinant Bet v 1 and birch extract groups do not differed significantly. This first comparison between the therapeutic efficacy of an immunotherapy between an extract and a major allergen show that SCIT with the recombinant allergen rBet v 1 is as effective and safe as treatment with natural birch pollen extract.

Besides Bet v 1, an additional immunotherapy trial with recombinant allergens was performed with the recombinant wild-type allergens Phl p 1, Phl p 2, Phl p 5a, Phl p 5b and Phl p 6 in patients with grass pollen allergy [48]. The double-blind, placebo-controlled, clinical trial enrolled 62 grass pollen-allergic patients with rhionconjunctivitis with or without asthma. The recombinant allergens were administered in subcutaneous injections at 7-day intervals before the pollen season, starting with 0.02 µg total protein, followed by 0.16 µg and then 40 µg of a mixture containing Phl p 1 10 µg, Phl p 2 5 µg, Phl p 5a 10 µg, Phl p 5b 10 µg and Ph1 p 6 5 µg as maintenance dose. The maintenance injections were continued until after the subsequent pollen season, with a 50% reduction during each pollen season. A symptom–medication score was the primary outcome measure to assess efficacy. A total of 24 actively treated patients and 25 placebo controls were evaluated. The primary end point showed a 39% improvement in the active treatment group compared with the placebo group. A validated rhinitis quality-of-life questionnaire was used as a secondary end point [49]. The overall benefit of the therapy after the second pollen season was significant. Conjunctival provocation tests were performed before therapy and at the end of the study using a standardized six-grass allergen extract, but statistically relevant differences between the two time points could not be detected.

Active treatment induced highly significant increases in IgG_1 and IgG_4 grass pollen-specific antibody concentrations together with a significant decrease in IgE. Four subjects in each group had no Phl p 5a- and Phl p 5b-specific IgE antibodies before therapy. None of these subjects developed IgE-specific antibodies to these allergens if tested at the end of the therapy; however, all developed strong IgG_4 and IgG_1 responses to Phl p 5a/5b, consistent with induction of a protective immune response. Unfortunately, the number of patients is too small to judge the risk of induction of new sensitizations during the therapy with a mixture of recombinant allergens in patients without specific IgE against a particular allergen structure before starting treatment. Such *de novo* sensitizations were reported to occur during SIT with allergen extracts [50,51] and could also represent a problem for the use of recombinant allergen mixtures in therapeutic trials involving large numbers of patients.

The most advanced clinical trials with a (modified) recombinant allergen have been reported for the ragweed-pollen allergen, Amb a 1, conjugated to a phosphorothioate oligodeoxyribonucleotide immunostimulatory sequence of DNA [52]. In spite of the enthusiasm generated by the analysis of the results obtained during the first treatments, Dynavax decided to discontinue a 2-year, multicenter study involving 738 ragweed allergic subjects (Dynavax Allergic Rhinitis TOLAMBA Trial [DARTT]) in February 2007 [105,106]. The reason for the study abandonment was that the selection of subjects was quite inadequate as both placebo- and active-treated groups were not displaying pronounced symptoms of ragweed allergy. We look forward to better-organized studies before a definitive evaluation of the efficacy of this vaccine can be drawn.

Peptide immunotherapy offers the potential to avoid IgE-mediated allergic reactions while targeting T-cell epitopes and inducing modulation of allergen-specific responses [53]. The majority of peptide immunotherapy studies in subjects with allergic disease have been performed with peptides derived from the major cat dander allergen Fel d 1 [54,55]. In addition, two small, open studies in bee venom-allergic subjects receiving an equimolar mixture of immunodominant T-cell epitopes derived from phospholipase A_2 (Api m 1, the major bee venom allergens [56]) have been reported [20,57]. The clinical studies showed that synthetic peptides representing T-cell epitopes of allergens have some potential to induce modulation of allergen-specific responses and, therefore, to be useful for the treatment of allergy, but larger dose-ranging studies testing larger groups of allergic individuals will be required before firm conclusions on clinical efficacy of peptide allergen therapy can be made.

Currently, the approach to modify B-cell epitopes to prevent IgE binding while preserving T-cell epitopes to retain the capacity for immunotherapy is quite fashionable. Obviously, the availability of single hypoallergenic variants for the most important allergens would be a great help to design vaccines with reduced side effects [58]. Recombinant allergens have been modified *in vitro* by site-directed mutagenesis to

create molecules with reduced IgE reactivity [59]. Although conceptually sound, site-directed mutagenesis of conformational IgE-binding epitopes is unlikely to help in this regard, mainly for economical reasons. We are dealing with hundreds of different allergen structures and, more importantly, with an unknown but much higher number of highly patient-specific IgE-binding epitopes [60,61]. What we need are more generalized cost-efficient approaches to generate allergen molecules useful for the treatment of large numbers of allergic individuals, independent from the patient-specific IgE-binding characteristics, without risk of anaphylaxis. Since most of the IgE-binding epitopes are conformational [62], an attractive method for producing hypoallergenic variants is to irreversibly prevent correct folding of the allergen molecules. Recombinant hybrid allergen proteins can fulfill this basic requirement and have the potential to be used as combination vaccines. These molecules consist of the most important epitopes contained in an allergenic source obtained either by fusing whole allergen sequences [63], polypeptides derived from the most important allergens [64] or allergens derived from different allergenic sources [65]. Although hypoallergenic isoforms [66], modified allergens with reduced IgE-binding capacity [67] and fusion allergens [63–65] have been tested successfully in animal models of allergy, it is, at present, unclear which of these approaches will be the safest and most efficacious in human clinical trials. Of course, safety of any new form of SIT will be a crucial issue for a successful establishment of future treatments.

The dream: light at the end of the tunnel?

During the first World Immune Regulation Meeting held in Davos, Switzerland, in April 2007, Kündig from the University of Zürich presented the results of an interesting clinical study later reported also at the 2007 EAACI congress in Goteborg, Sweden [68], which, if confirmed, could represent a breakthrough in the treatment of allergic diseases.

The study aimed at enhancing grass pollen SIT in hay fever patients by injecting the allergen directly into subcutaneous lymph nodes. The monocentric, randomized trial safety and efficacy study compared intralymphatic immunotherapy (ILIT) with only three low-dose grass pollen extract injections administered over 2 months with classical SCIT using 54 injection over 3 years. In total, 58 patients received ILIT and 54 received SCIT treatments. Therapy efficacy was evaluated after 4 months, 1 year and 3 years. Surprisingly, ILIT-treated patient showed a tenfold increase of the pollen concentration required to provoke nasal symptoms after only 4 months. Amelioration of allergy symptoms after three intralymphatic injections completed after only 8 weeks was long lasting and comparable with the amelioration achieved after 3 years of conventional SCIT. After 1 and 3 years follow-up, the ILIT group did not significantly differ from the SCIT group in terms of nasal provocation, use of rescue medication, subjective symptom amelioration, reduced reactivity to allergen extract in skin prick tests and decrease in allergen-specific serum IgE. However, only 32 out of 54 patients starting treatment finished the 3 years SCIT therapy. By contrast, all of the 58 patients randomized to the ILIT group received the full three injections treatment. Although these results need to be confirmed with larger numbers of patients and also with different allergen extracts, evidently, ILIT is more convenient for the patient and dramatically enhances compliance. A drastic increase in the patient's compliance is an absolute requirement to increase the market size of allergy vaccines, which would in turn facilitate allergy vaccine development programs.

An ulterior attractive approach to reduce the number of injections required to reach protection consists of the use of toll-like receptor (TLR) agonists, as summarized elsewhere [69]. Besides the use of the aforementioned immunostimulatory sequences [52], it has been shown that the use of monophosphoryl lipid A (MPL adjuvant, Corixa) as adjuvant can reduces allergic symptoms to grass pollen after only four preseasonal injections [70], approaching the 'dream' situation. However, the efficacy of TLR agonists also needs to be confirmed in large, multicenter clinical studies.

The reality

At a first glance, the market for allergy vaccines seems to be quite promising. The potential market size might even be larger for extrinsic asthma than for classical type I allergy. Approximately 300 million people worldwide currently have asthma [71], with estimates suggesting that asthma prevalence increases globally by 50% every decade [72]. It is recognized that approximately 70% of the people with asthma suffer from extrinsic (IgE-mediated) asthma [73]. Direct healthcare costs for asthma total more than US$9.4 billion annually; indirect costs (loss of productivity) add another US$4.6 billion for a total of US$14 billion per year in the USA alone [74]. In Europe, the total costs of asthma currently hover at approximately €17.7 billion per year, €9.8 billion thereof due to work impairment resulting in productivity losses [75]. In contrast to these huge numbers, the actual global marked size for SIT is, with an estimated total amount of approximately US$550 million [107], negligible. One of the problems in the development of allergy vaccines, especially if based on recombinant proteins, will be related to the development costs. According to recent estimates, the development of a new vaccine requires US$300–800 million [76], and this sum is not in relation with the current global annual market for allergy vaccines, which is in the same range. This might partly explain the discouragement of the industry to develop allergy vaccines, together with the fact that only a handful of the commercialized vaccines for infectious diseases have developed to blockbusters [77]. Moreover, it is difficult to come up with precise figures of the market size for a specific allergy vaccine. Allergic diseases are seldom life threatening and the severity of the symptoms covers a large scale ranging from mild short-term symptoms (e.g., in many cases of pollen allergy), to perennial severe symptoms (e.g., in allergic bronchopulmonary

aspergillosis, a very rare disease) [78]. Therefore, the prevalence of allergy against a given allergenic source, normally assessed by skin test reactivity in epidemiological studies, is not a reliable measure to assess the market size of a potential vaccine. However, prevalence multiplied with the population number, for example, of industrialized countries, acquire a degree of certitude that might give a false comfort. Such calculations are not sufficient to convince decision makers in pharmaceutical companies to invest in allergy vaccine development programs that, among many drug development programs, must compete with drug projects for funding. Drugs are more likely to yield a higher return of investment than vaccines and this is one of the main reasons why pharmaceutical companies are gradually abandoning vaccine-development programs [79]. From this point of view, there is no reason to be too optimistic about fast developments in the field of allergy vaccines because only big pharmaceutical companies have the expertise, facilities, experience, skill and financial resources required to develop such vaccines.

Expert commentary

In spite of considerable progress in understanding the mechanisms underlying a successful SIT, progress in clinical trials to improve allergic conditions is still moderate. SIT with allergen extracts applied as SCIT or SLIT undoubtedly provides a considerable alleviation of the allergic symptoms in most of the treated individuals but requires long-term treatment over years. As a consequence thereof, patients' compliance is low and the majority of the allergic individuals still choose symptomatic treatments to alleviate allergic symptoms.

First clinical trials based on recombinant allergens or peptides showed that vaccines based on single components or as a mixture of single recombinant allergens can be used to cure allergic diseases. However, these vaccines administrated subcutaneously mainly as aluminium hydroxide-adsorbed solutions do not contribute to shortening the treatment period and thus do not make allergy treatment more attractive for the patients.

SLIT self-managed at home [80] can be expected to have an advantage in acceptance over SCIT, which requires recurrent doctor's visits; however, SLIT also requires a long treatment period to reduce allergy symptoms. SLIT requires, as with SCIT, a high self discipline and perseverance to complete the recommended 3–5-year course of immunotherapy, limiting the number of patients choosing this form of therapy [12] and also resulting in a high number of dropout patients [81]. In my opinion, new routes of application, such as ILIT [68], perhaps combined with recombinant allergen vaccines able to target the MHC class II presentation pathway [82] and thus, resulting in an increased presentation of allergenic peptides [83], provide one of the most promising therapeutic strategies for the future. However, since these experimental vaccines have not yet entered Phase I clinical trials, it cannot be expected that they will penetrate the market before the end of this decade.

Five-year view

Unexpected breakthroughs excluded, I do not expect dramatic changes on the market situation of allergy vaccines during the next few years for several reasons. First, the time required to go from the bench to the clinics is quite long and expansive and those required to go from the first clinical trials to the market approval is even longer. Second, 'big' pharmaceutical companies that would have the capital required to develop allergy vaccines are, at present, not interested in entering this market segment. Third, the future legal regulations for marketing (allergy) vaccines are not clearly defined [77,79], limiting a rational calculation of the financial risk related to the development of allergy vaccines.

It can be expected that SLIT will expand the market size during the next few years owing to improved patient compliance and the possibility of using allergen extracts already approved for human use. This expansion will, however, probably reduce the market size for SCIT treatments in direct competition and will not contribute to a relevant reduction of treatment time.

As long as the total market size for SIT remains in the same order of magnitude as the amount of money required to develop a vaccine, we will not have the financial resources required for the development of alternative vaccination methods.

Of course, the long treatment period associated with the present forms of SIT are not favorable to encourage patients to choose this form of therapy, resulting in a stagnation of the market size.

In spite of the enthusiasm generated by the first clinical trials involving recombinant allergens, which allow the production of perfectly standardized therapeutic reagents, a realistic consideration of the state of the art shows that recombinant allergens have not yet contributed to reduce the treatment time, which still represents the major problem related to SIT. Moreover, vaccines based on recombinant allergens will end up in multicomponent vaccines to increase efficacy, further increasing developmental costs.

To increase the market size we should concentrate our efforts on the development of short-time therapeutic schedules, which, most likely, could contribute to increase the market size and, as a consequence thereof, generate higher rates of return of investment necessary for increasing the resources needed to intensify basic research as a catalyst for further progress. The use of TLR agonists might also contribute to substantially reduce the number of injections required for SIT [69,70] and, thus, help to achieve this goal.

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Key issues

- Reliable criteria for a stratification of the allergic patients entering clinical trials are required.
- Uniform end points for the judgment of the success of allergen-specific immunotherapy (SIT) according to the recently published guidelines should be used to allow comparison of the results obtained with the different therapeutic approaches.
- An improved international standardization of allergen extracts used for SIT is essential to ensure comparability of future clinical studies.
- Current strategies for the generation of allergy vaccines based on recombinant allergens are based on attempts to generate patient's tailored therapeutic reagents and to reduce allergenicity of the vaccines. These strategies do not contribute to a reduction of the long treatment time required to achieve protection.
- Intensification of the basic research devoted to elucidate the mechanisms governing SIT in concomitance with vaccine administration/scheduling is essential to further increase the efficacy of SIT vaccines. We particularly need to understand why protection conferred by SIT requires such a long time to establish.
- New routes of application, such as sublingual immunotheraphy, intralymphatic immunotherapy or mucosal applications should be carefully evaluated for their potential to increase patient's compliance or to achieve a relevant reduction of the treatment time.
- We need to increase the market size for SIT to generate higher returns of investment.

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