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Opinion

Vaccination against Allergy: A Paradigm Shift?

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Since the discovery that IgE antibodies mediate allergy, decades of research have unraveled complex mechanisms associated with conventional immunotherapy and the vital protagonists that shape 'immune tolerance' to allergens. Debate exists on what should constitute the dominant effector mechanism in driving rational drug designs for next-generation immunotherapies. As vaccine technology continues to advance, the development of novel vaccines in this area of continued medical need might stand on a threshold of breakthrough inspired by experiments by Dunbar on the passive vaccination of allergic animals more than 100 years ago. In this opinion article, we discuss both novel insights into IgG antibodies as the principle effector modality induced by specific immunotherapy and advances in antigen-carrier design that may catapult allergy treatment into our modern world.

Highlights

Recent advances in the use of virus-like particle (VLP) nanotechnology provides an optimal strategy for the treatment of allergy; eliminating the allergic potential of a vaccine while increasing its ability to trigger strong IgG reactions.

Modern approaches to allergen-specific immunotherapy (SIT) exploiting advances in antigen carrier systems such as VLP, aimed at maximizing IgG-mediated inhibition of allergen-induced mast cell activation, present a paradigm shift toward using a classical vaccination approach to treat allergy.

The translational potential of VLP technology in allergy may eventually be useful for prophylactic vaccination.

Allergy: From Orphan Disease to Pandemic

Allergic rhinitis, allergic asthma, and food **allergies** (see Glossary) are recently burgeoning diseases. The first documented case of hay fever occurred in 1819, when the physician, John Bostock, called the disease catarrhus aestivus (summer catarrh) [1]. Given that Bostock had the disease himself, this first patient was easily found; it took him more than 9 years to find another 28 cases, clearly demonstrating the scarcity of the disease rather than absence of reporting [2]. This has since dramatically changed and **IgE**-mediated allergies, such as allergic rhino conjunctivitis and asthma, have reached a worldwide prevalence of 25% [3], followed by food allergy, with a prevalence of ~10% [4]. Together with type 2 diabetes mellitus, they are called 'the new epidemics of the 21st century' [5]. This increase in prevalence is still rather poorly understood but evidence indicates a correlation with improved hygiene, altered nutrition, or reduced viral, bacterial, or parasitic diversity, or, more likely, it is a result of a complex interplay of all of these factors, summarized as the 'biodiversity hypothesis' [6]. In addition, epigenetic changes may additionally regulate the risk of developing allergies [7].

Potential Treatment for Allergies: From Symptomatic to Disease-Modifying Therapies

There are several ways to treat IgE-mediated allergies. The most accessible and commonly used therapies are symptomatic in nature and block the allergic reactions at the effector stage by inhibiting the action of histamine by using corticosteroids. While these therapies are effective, they usually need daily drug intake, which is not without chronic adverse effects if taken for years, and, most importantly, does not stop progression of the disease toward, for example, asthma. By contrast, **allergen-specific immunotherapy (SIT)** is the only disease-modifying therapy available [8,9]. SIT comprises repeated administration of specific **allergens** to patients with IgE-mediated allergies and results in protection against the allergic and inflammatory reactions usually associated with natural exposure to the same allergens [8]. The efficacy of SIT only recently became scientifically accepted subsequent to appropriate state-of-the-art double-blind, placebo-controlled trials. Indeed, it is now an established and medically preferred treatment option against respiratory allergies and hymenopteran venom allergy [8–11].

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Despite the clinical success of SIT, conventional long-course subcutaneous immunotherapy, typically formulated with an aluminum depot, remains cumbersome (e.g., monthly injections over 3 years) and the mechanisms of action remains unclear. To date, there are no validated and generally accepted candidate biomarkers that are predictive or indicative of the clinical response to conventional SIT [12]. It is recommended to explore the use of allergen-specific **IgG**4 as a biomarker for compliance. Serum IgE/total IgE and IgE-facilitated allergen binding (FAB) are considered as potential surrogate candidate biomarkers, although induction of increased **type 1 T helper cells (Th1)**, in particular **regulatory T cells (Tregs)**, has been postulated to mediate clinical efficacy [12]. More recently, additional immune cells, such as innate-like lymphocytes (ILCs) [13] and regulatory **B cells** [14,15], have also been implicated in SIT. However, in the absence of a clear effector mechanism, optimizing the therapy remains largely empirical and the primary endpoint in trials is based on subjective combined symptom and medication scores. Nevertheless, **adjuvant** systems, such as **microcrystalline tyrosine (MCT)** combined with monophosphoryl lipid A (MPL) [16–21] or **CpGs** (DNA rich in non-methylated CG motifs, a ligand for TLR9) in free form [22] or packaged into **virus-like particles (VLPs)** [23,24], have been tailored in formulations that have achieved evidence of efficacy in fewer doses compared with conventional treatments and may offer new opportunities in identifying novel biomarker candidates. Formulating the allergens with depot adjuvants or the use of allergoids, which exhibit chemically modified epitopes, are also ways to increase the dose but maintain tolerability [24,25]. Several novel approaches to develop next-generation allergen immunotherapies have been further explored. Such approaches include novel microbiome applications, peptide immunotherapy, intralymphatic immunotherapy, epicutaneous immunotherapy, and the use of nanoparticles with or without native allergens [23,24,27–30].

Many lessons may be drawn from the successes in vaccinology; thanks to new technologies, vaccines are on a path to revolutionize the health of the modern population [31,32]. More than 100 years ago, allergen immunotherapy was described in a way that drew parallels with vaccinology at this time, described as 'a prophylactic vaccination against hay fever' [33]. Upon the discovery of IgE and research to further elucidate the rather complex interplay of immunological mechanisms that mediate allergy and conventional SIT, those fundamental parallels with vaccinology ('a vaccine against toxins') were somewhat lost and subsequent research focused on the idea that SIT should 'induce tolerance', dampening IgE reactivity [34]. However, the design of several new technology platforms has revived the concept that allergens may be viewed as 'protoxins', highlighting the importance and protective umbrella of neutralizing antibodies, which is now considered to be broader than first appreciated [34,35].

Here, we discuss allergen-specific IgG antibodies, which may be considered a key effector modality in SIT; allergens displayed on VLP, which are highly immunogenic but do not induce anaphylactic reactions; the induction of IgG antibodies against a single allergen combined with VLP nanoparticles to protect against a complex allergen cocktail. The growing evidence in using advanced nanoparticle technology reviewed herein considers a paradigm shift toward a classical vaccination approach to treat allergy (see Clinician's Corner).

Allergen-Specific IgG Antibodies Are the Key Effector Modality in SIT

SIT induces a change in T cell subtypes, mainly Tregs and a shift from **type 2 T helper cells (Th2)** to Th1 cells [36,37]. While induction of Tregs appears to be transient, a reduction in Th2 cell activity is more long-lasting [38]. Both Th1 and Tregs are thought to block Th2 cells, causing a non-allergic milieu and depletion of IgE synthesis in the long term (Figure 1A). In addition to a change in T cells, SIT induces allergen-specific IgE and IgG. Allergen-specific IgG production may often depend on the induction of regulatory B cells, which also secrete immune-suppressive cytokines [14,15].

Glossary

Adjuvant: a substance that enhances the immune-stimulating properties of an antigen or the pharmacological effect of a drug.

Allergen-specific immunotherapy (SIT): also known as desensitization or hyposensitization; the most common form of specific immunotherapy; involves a course of injections that build up tolerance to particular allergens through small, controlled doses.

Allergens: proteins that trigger the immune system of an allergic person to produce unwanted symptoms.

Allergy: a chronic condition involving an exaggerated reaction to an otherwise harmless substance, called an allergen.

B cells: differentiate into clones of antibody-producing plasma cells; have a central role in allergen tolerance through the production of IgG-blocking antibodies.

CpG: oligonucleotides enriched in CpG motifs are potent immunopotentiators of dendritic cells and B cells.

$Fc_{\varepsilon}RI$: a high-affinity IgE receptor expressed on the cell surface of mast cells and basophils; triggers the IgE-mediated allergic cascade.

$Fc_{\gamma}RIIb$: a low-affinity IgG receptor. IgG antibodies can inhibit IgE-mediated mast cell activation through direct allergen neutralization or through the inhibitory receptor FcγRIIb.

IgE: primary antibody mediator in the allergic response.

IgG: most common antibody in the body; used to treat a range of diseases.

Mast cells: similar to basophils, mast cells become activated by antigen crosslinking of $Fc_{\varepsilon}RI$ receptor-bound IgE to undergo rapid degranulation and release of the inflammatory substance histamine, causing an allergic reaction.

Microcrystalline tyrosine (MCT): a depot adjuvant.

Pathogen-associated structural pattern (PASP): a pathogen-associated molecular pattern (PAMP). Cells of the innate immune system utilize pattern recognition receptors to identify viral pathogens by engaging PAMPs.

Regulatory T cells (Tregs): involved in preventing sensitization to allergens by suppression of T cell responses to T cell epitopes of major allergens.

T helper (Th) cell: also known as CD4+ cells; a type of T cell that help the activity of other immune cells by releasing T cell cytokines. These cells help suppress or regulate immune responses. For

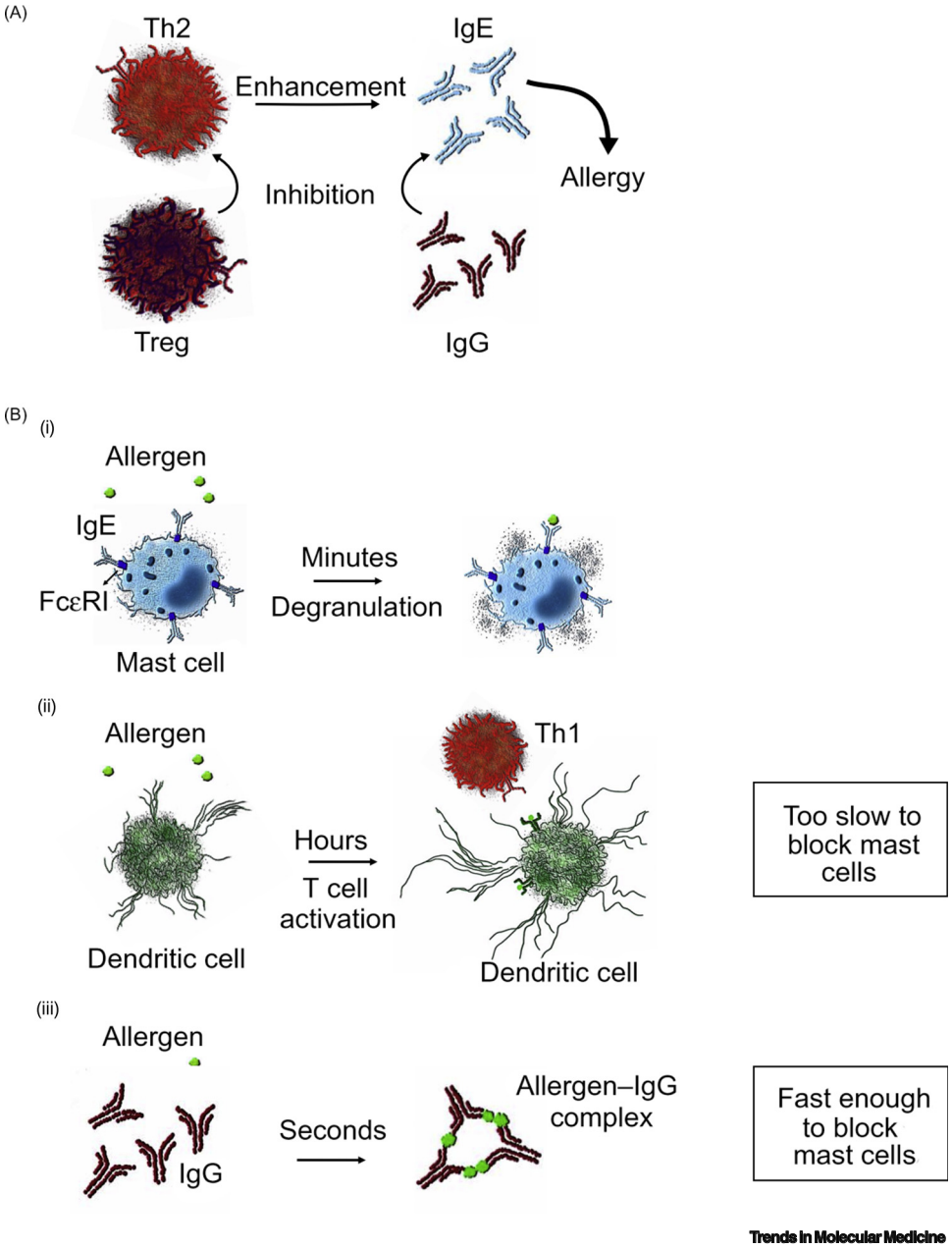

Figure 1. Kinetic Considerations in the Regulation of Allergic Responses. (A) Type 2 T helper cells (Th2) enhance the activation of an IgE-mediated allergic response. Regulatory T cells (Tregs) inhibit IgE production indirectly via inhibiting Th2, while allergen-specific IgG directly inhibits IgE via different mechanisms. (B) (i). Allergens crosslink IgE molecules bound to the surface of tissue mast cells, which rapidly triggers degranulation and the release of preformed mediators, including histamine, within minutes. (ii) Antigen uptake and processing by dendritic cells for T cell activation requires hours rather than minutes, which presents a kinetic disadvantage. (iii) Allergen-specific IgG are able to bind and block allergen-induced cellular activation within seconds.

example, they are essential in B cell antibody class switching.

Type 1 T helper cells (Th1): mediate cell-mediated immune responses to intracellular pathogens, such as viruses, bacteria, or tumor antigens.

Type 2 T helper cells (Th2): allergen-specific Th2 responses have a pivotal role in the activation and/or recruitment of IgE antibody-producing B cells, mast cells, and eosinophils.

Virus-like particles (VLPs): molecules that closely resemble viruses, but are non-infectious because they contain no viral genetic material. They can be naturally occurring or synthesized through the individual expression of viral structural proteins, which can then self-assemble into the virus-like structure.

One million-fold more IgG than IgE (milligrams per milliliter versus nanograms per milliliter) circulate in the bloodstream, and allergens are likely to form complexes with polyclonal IgG antibodies of several specificities before they reach **Fc$_\varepsilon$RI-**bound IgE [39].

IgG4, the least-represented human IgG subclass in serum, is an intriguing antibody with unique biological properties, such as the ability to undergo Fab-arm exchange and to limit immune complex formation. The lack of effector functions, such as antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity, is desirable for therapeutic purposes. IgG4 has a protective role in allergy by acting as a blocking antibody (Figure 1A), and inhibiting **mast cell** degranulation [40] Furthermore, crosslinking of **Fc_{γ}RIIb** by the IgG4 subclass redirects proallergic M2a macrophages to an M2b-like immunosuppressive phenotype. This suggests an interplay of macrophages with IgG4 in immune tolerance, likely relevant in allergen immunotherapy [41].

The Mechanisms of SIT Revisited: Th1 and Tregs

Allergen-specific IgE induction occurs early after treatment and is transient ,while IgG responses are long lasting. Importantly, the increase in IgG is more prominent than the long-term reduction in IgE levels; in addition, a reduction in IgE does not always occur [42]. Hence, the effector mechanism induced by SIT must be able to block allergic responses despite the presence of allergen-specific IgE. As discussed previously [34], this renders Tregs and Th1 cells unlikely candidates mostly for kinetic reasons. Indeed, allergic symptoms in hay fever occur within minutes and, therefore, cannot be blocked by antigen-specific T cells, which are activated by the recognition of allergen-derived peptides presented on MHC class II molecules (Figure 1B). Processing allergens for antigen-presentation requires hours rather than minutes, excluding sufficiently rapid activation of T cells to block IgE-mediated mast cell or basophil activation (Figure 1B). It may be argued that Tregs create a non-inflammatory milieu; however, such a mechanism would not be allergen specific and, therefore, is not compatible with clinical experience [34,43,44]. In addition, depletion of Tregs in a murine model of cat allergy did not abrogate protection induced by SIT [45]. In contrast to slowly activated allergen-specific T cells, allergen-specific IgG may be able to block allergen-induced cellular activation within seconds (Figure 1B).

The Mechanisms of SIT Revisited: Antibodies

It is well established that SIT induces allergen-neutralizing IgG antibodies [38,42] and that these antibodies are able to block IgE-mediated antigen presentation. Even though induction of IgG does not always correlate with clinical efficacy [12], the IgE:IgG ratio might be the more important parameter yielding better correlations or, indeed, considerations related to the affinity and/or avidity of IgG4 and ELISA-based approaches to establish a meaningful correlation [12]. In a classical experiment, immune sera from patients after but not before SIT were able neutralize allergens in a skin-prick test, directly demonstrating the therapeutic potential of allergen-specific IgG [46]. Furthermore, it has been shown in murine models of cat and peanut allergies that the transfer of allergen-specific IgG resulted protection against local and systemic allergen challenge [35,47]. An important piece of evidence for a protective role of allergen-specific IgG was recently provided in a clinical study that demonstrated that passive vaccination with monoclonal antibodies (mAbs) against Fel d 1, the major allergen in cats, protected humans against allergic symptoms [48]. Thus, such evidence resuscitates the concept from the early 20th century developed by the American physician Dunbar using antibody-based immunotherapy [49,50].

IgG antibodies may block mast cell and/or basophil activation via three pathways: direct allergen neutralization (Figure 2A); engagement of the inhibitory Fc_{γ}RIIb (Figure 2B) [51]; and co-internalization of IgE by mast cells (Figure 2C) [52]. Direct allergen neutralization is the most straightforward mechanism, because it simply blocks the access of the allergen to IgE bound to the high-affinity Fc RI (Figure 2A).

However, allergen neutralization is demanding since the antibodies essentially need to block all epitopes recognized by IgE. It was recently shown that only high-affinity antibodies are able to

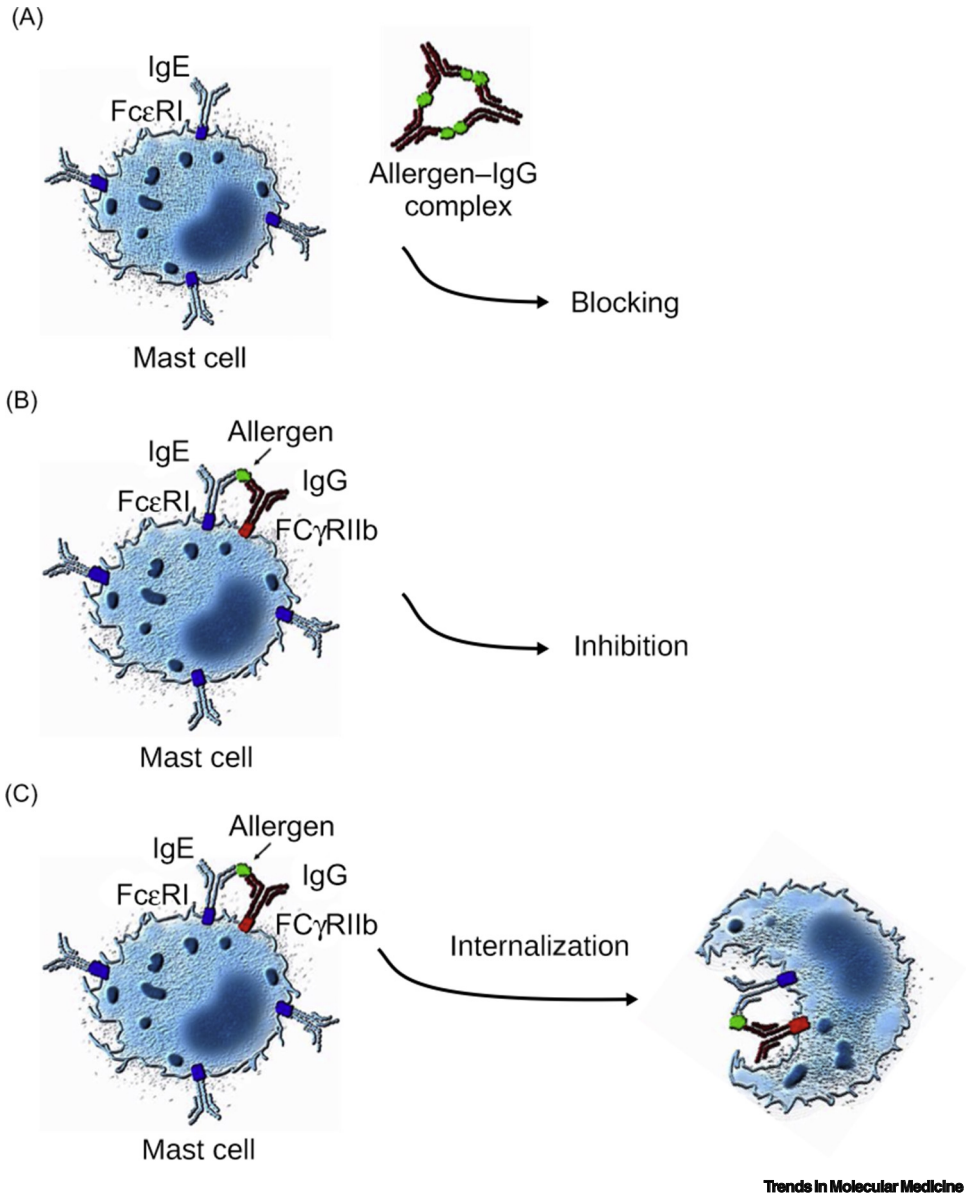

Figure 2. Inhibition of Mast Cell and/or Basophil Activation. IgG antibodies can block mast cell activation via three main pathways. (A) Allergen-specific IgG antibodies can directly neutralize the allergen by forming allergen–immune complexes and blocking their access to IgE bound to the high-affinity Fc RI. (B) Engagement of the inhibitory receptor Fc_{γ}RIIb by IgG–immune complexes blocks mast cell activation. (C) Allergen-specific IgG interacts with Fc_{γ}RIIb and promotes IgE internalization, which inhibits mast cell activation.

mediate allergen neutralization [35]. By contrast, engagement of the inhibitory receptor Fc_{γ}RIIb by an IgG-allergen immune complex is sufficient to block cellular activation. Hence, this mechanism is less demanding because not all epitopes need to be targeted. Furthermore, and rather unexpectedly, antibodies with affinities as low as 10^{-7} M effectively shut down mast cell activation [35]. Hence, in contrast to neutralizing antibodies, Fc_{γ}RIIb-engaging IgG antibodies can be of low affinity. Engagement of Fc_{γ}RIIb causes its internalization and it was recently shown that co-engaged IgE is co-internalized [52]. Hence, co-exposure to allergen and specific IgG causes the removal of IgE from the surface of mast cells.

'Trans-inhibition', a previously unreported regulatory mechanism by which antibodies can energize mast cells and basophils when engaging Fc receptors, operates in normal primary mast cells and basophils, whether of murine or human origin, and human $Fc_{\gamma}RIIb$ induces trans-inhibition similarly to murine $Fc_{\gamma}RIIb$. Trans-inhibition dampened all IgE-induced mast cell secretory responses, including the release of all mediators that account for anaphylaxis. Interestingly, whereas all ITIM-containing receptors can inhibit activation signals in *cis*, $Fc_{\gamma}RIIb$, but not other ITIM-containing receptors, can inhibit signaling in *trans* [39].

IgG4 antibodies exhibit blocking activity, as might IgG1 antibodies [53]. Thus, the ability of mAbs of the IgG1 and IgG4 isotypes to neutralize allergens and to engage $Fc_{\gamma}RIIb$ should be further investigated. Using recombinantly produced murine antibodies, it was recently shown in mice that IgG1 and IgG2a antibodies of the same specificity were equally potent at inhibiting the allergic reaction [52].

In summary, these observations clearly illustrate the potential of allergen-specific IgG antibodies to protect against allergic symptoms. While these results do not exclude a potential role for T cells in SIT, they demonstrate that induction of IgG alone may be sufficient for clinical efficacy. Thus, it is reasonable to rationalize a next-generation SIT based on the induction of high levels of IgG antibodies without causing adverse effects of the allergen used for vaccination. We discuss in the next section how displaying allergens on VLPs enables a repertoire of B cells to be induced to generate more robust and sustained allergen-specific IgG as a principle effector modality for next-generation allergy vaccines.

Allergens Displayed on VLPs Induce Strong IgG Responses but Are Unable to Elicit an Allergic Response

VLPs are multiprotein supramolecular structures with most of the characteristics of viruses other than they are unable to replicate [54]. Most VLPs have a shell constructed of several identical protein copies forming icosahedral or helical (rod-shaped) structures [55,56]. There are several VLP-based vaccines on the market, including vaccines against Hepatitis B, Human Papilloma Virus, and malaria [54]. The high immunogenicity of VLPs is based on several factors. A key feature of VLPs is their rigid and repetitive structure, which is a unique feature of viral and bacterial surfaces and, hence, considered to be a **pathogen-associated structural pattern (PASP)** [57,58]. Repetitive and rigid surfaces are ideal to crosslink B cell receptors and for the recruitment of the innate humoral immune system, in particular natural IgM activating the classical complement cascade [59]. This is turn increases the deposition of VLPs on follicular dendritic cells, enhancing germinal center formation in a B cell and complement receptor-dependent fashion [60]. In addition, engaging the complement receptor CD21 on B cells enhances the formation of long-lived plasma cells [61,62].

Some RNA virus-derived VLPs have an additional seminal feature: they package RNA from the cellular system that was used for expression. This RNA serves as a ligand for TLR7/8, drives isotype switching to IgG and IgA [63], and renders IgG responses independent of IL-21 [64]. Furthermore, the presence of RNA drives the generation of secondary plasma cells, which produce IgG antibodies at increased levels compared with plasma cells generated during primary antibody responses [65]. Importantly, the potency of the RNA-driven TLR7/8 signals varies with the system used for expression, with bacterial RNA being superior to eukaryotic RNA [66].

A immunologically optimized VLP platform based on Cucumber Mosaic Virus (CuMV-VLPs) was recently reported [67]. These plant virus-derived VLPs are produced in *Escherichia coli* and package bacterial RNA. Given that **Th cell**-dependent IgG responses are usually limited by the presence of Th cells rather than B cells, a universal Th cell epitope derived from tetanus toxin (TT) was introduced into the VLPs, resulting in CuMVtt. Given that most humans are immunized against TT

and recognize the universal T cell epitope, this modification is expected to enhance IgG responses throughout the human population. Importantly, this CuMVtt platform can be used to display antigens on the VLP surface, usually by chemical conjugation of peptides or proteins. This renders the conjugated epitopes immunogenic on the underlying VLP surface [67]. Using this platform, clinically efficacious therapeutic vaccines targeting IL-31 in dogs [68], IL-5 in horses [69,70], Fel d 1 in cats [71], and pain in mice [72] have been reported. More recently, a vaccine against peanut allergy based on CuMVtt was developed [47], comprising Ara h 1 or Ara h 2 chemically conjugated to the surface of CuMVtt. A similar technique was used to display recombinant Fel d 1 on the surface of an RNA phage-derived VLP Qβ [73]. In both cases, allergens displayed on the VLPs were more immunogenic than their free counterparts. In addition, a Der p 1-derived antigen also showed strongly enhanced immunogenicity in mice and humans if displayed on VLPs [74]. More surprisingly, however, while free allergens triggered local and systemic allergic reactions *in vivo* and caused basophil activation *in vitro*, allergens displayed on VLPs failed to do so. In fact, they completely failed to induce an allergic reaction *in vivo* and their ability to cause basophil and mast activation *in vitro* was attenuated by orders of magnitude, as illustrated in Figure 3 [73,75]. This was not due to the absence of epitope accessibility on the allergens

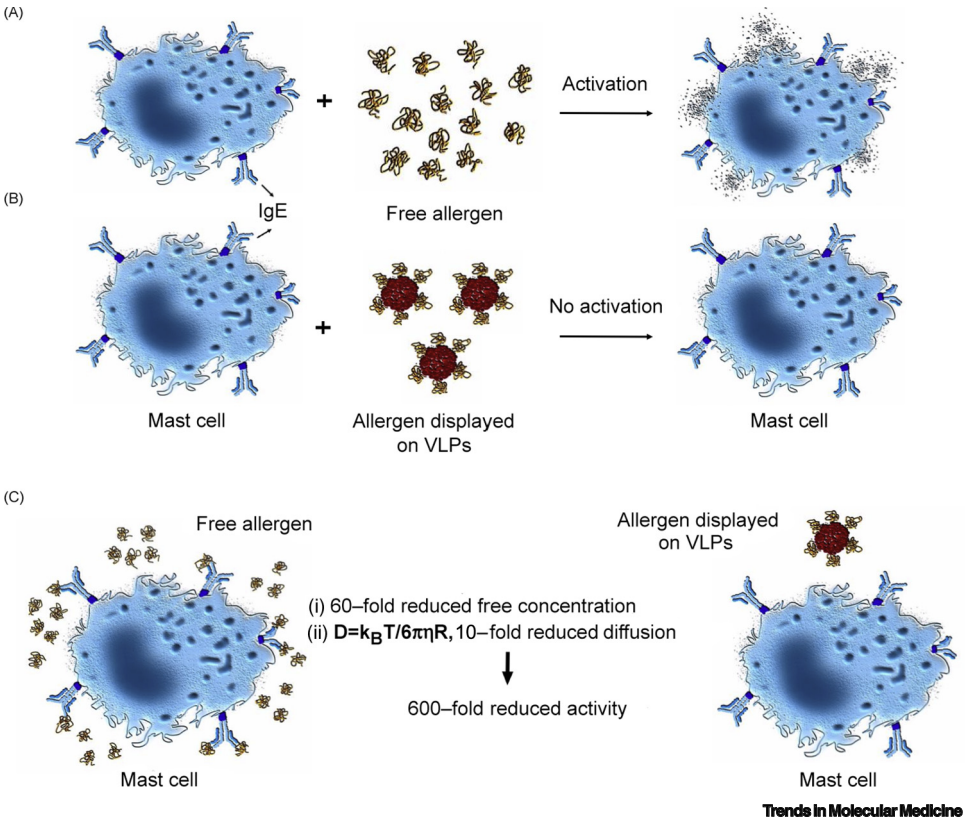

Figure 3. Making the Allergen Look Like a Virus Eliminates IgE-Mediated Activation of Mast Cells [75]. (A) Freely dispersed allergen portrays a more favorable diffusion gradient and is more likely to come into contact with surface-bound IgE. (B) An allergen displayed on virus-like particles (VLPs) fails to activate mast cells, which can be explained in relation to the size, geometry, and kinetics of VLPs. (C) Assuming a 40 kDa allergen attached to a 4MDa particle, the diffusion coefficient is reduced by a factor of ten, according to the Stoke-Einstein equation, where D is the diffusion constant; μ is the "mobility", or the ratio of the particle's terminal drift velocity to an applied force, μ = vd/F; kB is Boltzmann's constant; T is the absolute temperature. Combined with the 60-fold lower effective free concentration of allergen displayed on VLPs, a process that is driven by diffusion is about 600-fold lower for the VLP-allergen, than for freely dispersed allergen(s).

displayed on VLPs because these allergens were recognized by mAbs and induced allergen-neutralizing IgG responses *in vivo*. Interestingly, similar findings have been made for cytokines displayed on VLPs, which readily induce neutralizing antibodies but do not cause an inflammatory response [76–78].

There are two explanations for this finding: a physicochemical one and a biochemical one. From a physicochemical point of view, allergens attached to a VLP are highly concentrated locally. On average, ~60 allergens are attached to a VLP, reducing the effective free concentration of allergen by a factor of 60. In addition, they are attached to a 4-MDa particle. According to the Stoke–Einstein equation, the diffusion coefficient of a molecule is inversely proportional to its size, which means that, for a 40-kD molecule attached to a 4 MDa particle, the diffusion coefficient is reduced by a factor of ten. Thus, the effective allergen concentration is reduced by a factor of ~600 if attached to a VLP [75]. From a biochemical point of view, repetitively displayed allergens are inefficient at activating mast cells. Indeed, even if allergens on VLPs bind to mast cells, they fail to trigger cellular activation [75]. Most likely, this is related to the observation that a too high allergen concentration fails to activate mast cells, a phenomenon known as bell-shaped mast cell activation, where too much crosslinking appears to be inhibitory. This is different for B cells, which are optimally activated by repetitive antigens spaced apart by 5–10 nm. The biological explanation for this difference is that B cells are mostly geared to respond to pathogens, which often are particulate and have a repetitive surface, while mast cells respond to soluble proteins.

Thus, displaying allergens on VLPs greatly enhances their immunogenicity but abrogates their ability to induce a type I allergic reaction, combining important efficacy and safety features. As such, this approach provides an attractive option for developing new vaccines in areas of disease, such as allergy, which may provide an optimal approach to optimizing safety and efficacy.

Induction of IgG Antibodies Against a Single Allergen is Sufficient to Protect Against a Complex Allergen Cocktail

Use of a single allergen approach, combined with VLPs, has indicated a strong proof of principle in preclinical models and in humans. For example, a protective effect of allergen-specific IgG was obtained by the administration of two monoclonal Fel d 1-specific IgG antibodies in patients with a cat allergy, who showed significantly improved symptoms after nasal stimulation tests in a placebo-controlled trial [48]. Vaccination with a peptide antigen [derived from the house dust mite (Der p 1)] covalently coupled to highly repetitive VLPs rapidly induced high IgG antibody titers in patients [74]. In this study, all individuals showed strongly increased titers from 14 weeks up to 18 months, while reporting a good safety and tolerability profile, in line with other VLP-based trials.

More recently, it has been shown in murine models of cat and peanut allergy that the transfer of allergen-specific IgG resulted protection against local and systemic allergen challenge [34,47], drawing parallels with those early experiments by Dunbar using antibody-based immunotherapy [49,50].

The use of a modern VLP nanotechnology platform, optimized for B cell induction using the Cucumber Mosaic Virus is currently in development, with first-in-human trials planned[i]. The preclinical safety and efficacy proof of concept recently reported demonstrated a sufficient titer of IgG antibodies with adequate affinity and/or avidity for the allergen, and was able to diminish allergic symptoms after exposure. In this study, a significant increase was observed in specific IgG responses after combining the Cucumber Mosaic VLP with a single peanut major allergen [47]. Active immunization against a single allergen (Ara h 1 or Ara h 2) resulted in protection against

Clinician's Corner

A crucial goal for SIT is to design and produce a next-generation immunotherapy that has a favourable safety profile but provides long-term protection and induction of long-lasting immune responses. The key properties of viruses that facilitate the induction of potent immune responses may be used as the basis for rational vaccine design.

The VLP-induced B cell response from preclinical and early clinical studies in allergy is intriguing and provides a realistic aspirational goal as a disease-modifying treatment.

Food allergy, particularly peanut allergy, is an area of continued medical need where the most common approach to management is strict avoidance, which is inadequate. Treatment modalities, such as Oral Immunotherapy, frequently involve daily administration and the risk of severe adverse reactions remains [26].

Safety is the foremost requirement for any new vaccine in the field of allergy. The unique and inherent properties of VLPs allow for controlled presentation of allergens to the immune system to enhance vaccine safety, while extending a broad and cross-reactive protective umbrella of IgG from memory B cells not thought possible previously.

systemic, local, and oral challenge with peanut extracts, comprising multiple allergens in a sensitized mouse model. Hence, immunization against a single allergen resulted in protection against the complex allergen challenge [47]. Passive immunization demonstrated that transfer of purified IgG fractions could confer protection against allergic reactions [47]. This supports the role of IgG in the mechanism of protection induced by the vaccine candidate (Figure 4). Furthermore, the inhibitory receptor $Fc_{\gamma}RIIb$, present on mast cells and basophils ,was critical for reduced allergic symptoms. These results are in line with previous studies showing that $Fc_{\gamma}RIIb$ was able to inhibit signals generated by activating receptors that were sensitized with non-crossreacting IgE and were not directly co-engaged with FcγRIIb [34,79].

The VLP-specific B cell response from preclinical and early clinical studies, in the absence of additional adjuvants, are of significance. However, VLPs loaded with CpGs have been shown to provide benefit ,and the combination of VLPs with microadjuvants, such as MCT, has been shown to confer added benefit through the induction of T cells [80]. Thus, such an approach is subject to further studies investigating the added benefit in terms of T cell support, with scope to help further optimize clinical outcomes.

Concluding Remarks

Advances in the study of novel antibody and nanoparticle antigen-carrier designs, such as VLPs, have renewed interest in the concept of targeting B cells as the primary modality for next-generation SIT, drawing upon advances in vaccinology. The fact that immunizing against a single allergen protects against an allergen mixture is striking and could be applied against different

Outstanding Questions

Large-scale double-blind, placebo-controlled trials are needed to understand the translational potential of allergen-specific VLPs and their clinical properties, including the contribution of sustained clinical effect by IgG subclasses and their protective umbrella.

In terms of IgG-mediated inhibition of allergen-induced mast cell activation, the presence of this receptor on human basophils is well characterized. However, the characterisation of $Fc_{\gamma}RIIb$ on human mast cells is less clear and should be further studied.

The prophylactic potential of using VLP-based vaccination in allergy should be further tested and assessed in the clinical setting in individuals who are at risk of developing allergies.

An adjuvant systems approach using VLPs with other compatible adjuvants may optimize clinical outcomes, although understanding the immunological benefit and safety profile will be key.

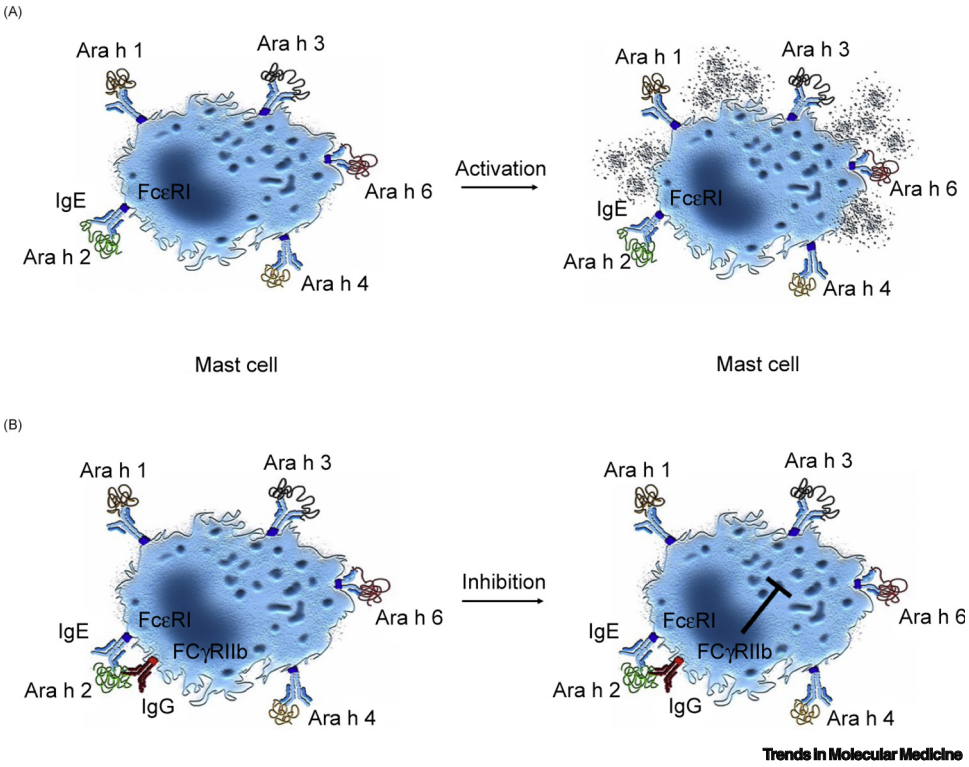

Figure 4. Inhibition of Mast Cells by $Fc_{\gamma}RIIb$ in a Model of Peanut Allergy (Ara h 1). In presence of high levels of IgG antibodies specific for a single allergen, IgG–immune complexes are formed and bind $Fc_{\gamma}RIIb$, inhibiting all IgE-mediated signals, including those from IgE molecules crosslinked by other allergens.

relevant allergies that are frequently caused by sensitization against more than one allergen [47]. These advances allow a new platform and approach to allergy treatment that promises to effectively balance safety and efficacy, while providing a well-defined and standardized product. Novel insights into IgG antibodies as the principle effector modality induced by SIT provide a stronger footing than ever before, which has already been reflected in promising preclinical and first-in-human trials, which are now planned to be extended, enabling a deeper understanding of the translational potential of allergen-specific VLPs and their clinical properties. Large-scale double-blind, placebo-controlled trials are also needed to understand the translational potential of allergen-specific VLPs and their clinical properties, including the contribution of sustained clinical effect by IgG subclasses and their protective umbrella (see Outstanding Questions). An adjuvant systems approach using VLPs with other compatible adjuvants may optimize clinical outcomes, but understanding the immunological benefit and safety profile will be key. In terms of IgG-mediated inhibition of allergen-induced mast cell activation, the presence of this receptor on human basophils is well characterized, although further studies are required to fully determine and characterize the presence of FcγRIIb on human mast cells.

Disclaimer Statement

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Resources

[i]http://ir1.q4europe.com/IR/Files/RNSNews/476395/AllergyTherapeutics2018TF_14586336.pdf

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