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REVIEW ARTICLE

Novel approaches for allergen-specific immunotherapy—An overview

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ABSTRACT

Allergen-specific immunotherapy (AIT) is an allergen-specific treatment for people with IgE-related allergies. Allergen-specific immunotherapy (AIT) is used to treat allergic disorders when symptoms persist despite medication and allergen avoidance. The therapy is presumed effective if it reduces the use of medications, improves the quality of life even after discontinuation of treatment, as well as prevents the conversion of one type of allergy to the other and the development of new sensitization. The allergen-specific immunotherapeutic agents can be administered sublingually, subcutaneously, or through some other routes, such as intra-lymphatically and epicutaneously to induce allergen tolerance by modifying immune responses (innate and adaptive). The primary mechanism of AIT is the induction of functional regulatory cells, such as regulatory T cells, follicular T cells, B cells, dendritic cells, innate lymphoid cells, and natural killer cells, which results in the control of the functions of type 2 inflammatory cells. However, there are several downsides to AIT, including the contentious treatment period resulting in high cost, systemic allergic reactions, and the lack of a biomarker for forecasting treatment responders. Vaccine adjuvants, adjunctive therapies, and novel vaccine technologies are currently being researched to address the issues associated with AIT. This article focuses on defined molecular approaches for improving the potential of specific immunotherapy that use recombinant allergen derivatives, allergen-derived peptides, virus-coupled allergens, nanoparticles, and specific adjuvants.

Keywords: Immunotherapy; Allergy; Allergen-specific Immunotherapy; T Cells; Dendritic Cells; Immune Responses; Allergen-derived Peptides; Adjuvants

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1. Introduction

An allergy is a type I hypersensitivity reaction that happens when the immune system responds to a non-self agent in a harmful way or even kills the person. The non-self agent or antigen causes an immune response (either mediated by IgE antibodies or not mediated by IgE antibodies) that sets off a chain of molecular and cellular events that lead to the symptoms of an allergic reaction. The response can be split into two parts: the immediate phase, which is mostly caused by IgE, and the late phase, which is caused by inflammatory markers and cytokines. Both of these stages are included in the term "immediate hypersensitivity", which is clinically known as "allergy"[1]. Conjunctivitis, rhinitis, asthma, urticaria, atopic dermatitis, and angioedema are a few examples of tissues where the symptoms may manifest. Other symptoms may impact the entire body and be followed by a lowering in blood pressure (anaphylaxis)[2].

The terms "hypersensitivity" and "allergy" are used interchangeably. Depending on the effector mechanism and type of immune response causing tissue and cell damage, allergies are frequently categorized. Phillip Gell and Robin Coombs, two Brit-

ish immunologists, created this categorization in the early 1960s[3]. There are four different categories of hypersensitivity reactions, according to Gell-Coomb hypersensitivity labels (**Figure 1**)[4–7]:

Type-I: anaphylactic hypersensitivity, **Type-II:** cytotoxic hypersensitivity, **Type-III:** immune complex hypersensitivity, and **Type-IV:** delayed or cell-mediated hypersensitivity.

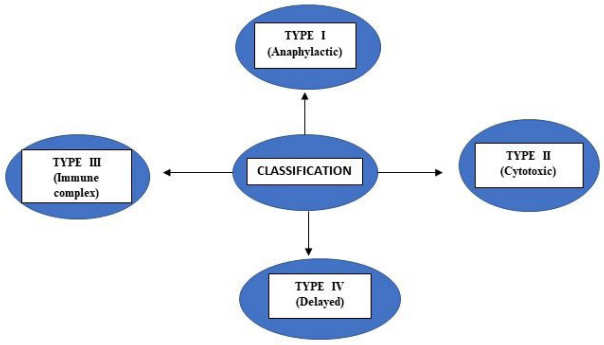

Figure 1. Classification of hypersensitivity reactions.

Type I (Anaphylactic hypersensitivity)

The initial sensitivity brought by an IgE antibody is known as type I hypersensitivity. A type I hypersensitivity reaction happens when an antigen forms a cross-link with the mast cell or basophil carrying the membrane-bound IgE antibody. Histamine is released after an allergic reaction, which may result in tissue damage. Urticaria and angioedema are two examples of IgE-mediated medication responses involving the skin. When IgE is involved, severe reactions can sometimes be fatal, as in the case of anaphylaxis.

Type II (Cytotoxic hypersensitivity)

Immunoglobulin G (IgG) or Immunoglobulin M that is drug-specific (IgM) antibodies mediate the reaction. After particular IgG or IgM antibodies are targeted against drug-like hapten on their cells, people experience immune-allergic cytopenia, anemia, and thrombocytopenia. Examples of medications include methyldopa, penicillins, and hydralazine.

Type III (Immune complex hypersensitivity)

These are controlled by soluble immune complexes that combine antibodies and antigens. Complement activation and inflammation are caused by tissue sedimentation of drug-antibody tangled, particularly in the kidney, joints, artery walls, skin, and lung (i.e., arthralgia, serum sickness, etc.). Sulphonamides, hydralazine, Penicillins, procainamide, and various monoclonal antibodies are some examples of medications.

Type IV (Cell-mediated or delayed hypersensitivity)

Also called a type of delayed hypersensitivity that depends on antigen interaction with T lymphocytes. IFN constitutes one of the cytokines responsible for the initial stages of type IV hypersensitivity, using lymphocytes and macrophages as markers of erythema and edema.

Traditional approaches

Leukotriene antagonists, bronchodilators, and steroids are some of the frequently used traditional therapies for allergic asthma[8]. All of these drugs have imperfections, notably effectiveness, side effects, and high cost. The development of novel therapeutic strategies for the management of allergic illnesses is becoming more and more essential nowadays, and the present review emphasizes allergen-specific immunotherapy.

2. Allergen-specific immunotherapy

Allergen-specific immunotherapy (ASIT), the preferred therapy available for IgE-mediated allergy, has been used to treat allergic patients for more than a century. AIT's disease-modifying effects result in reduced disease intensity as well as usage of the drug, avoidance of upcoming allergen sensitization, and a prolonged curative result. To date, the sensitizing allergen has generally been administered in ascending doses (subcutaneous, sublingual, oral, or epicutaneous) until a high enough dose is obtained and sustained to provide long-term therapeutic benefit from AIT. Allergen-specific immunotherapy (ASIT) does not affect allergen-specific Type 1 T helper (Th1) cells/Type 1 regulatory (TR1) cell responses. It has been reported that the primary mechanism controlling the alteration in Th1/Th2 allergen-specific T cell ratios and the restoration of allergen tolerance during immunotherapy is a preferential deletion of allergen-specific Th2 cells. Overall, the findings of the reported research provide light on what is considered to be the main cause of ASIT and offer new strategies for creating better allergy vaccines[9].

2.1 Mechanism

Antigen-presenting cells (APCs), such as dendritic cells (DCs), are thought to play a crucial role in eliciting an allergic immune response by con-

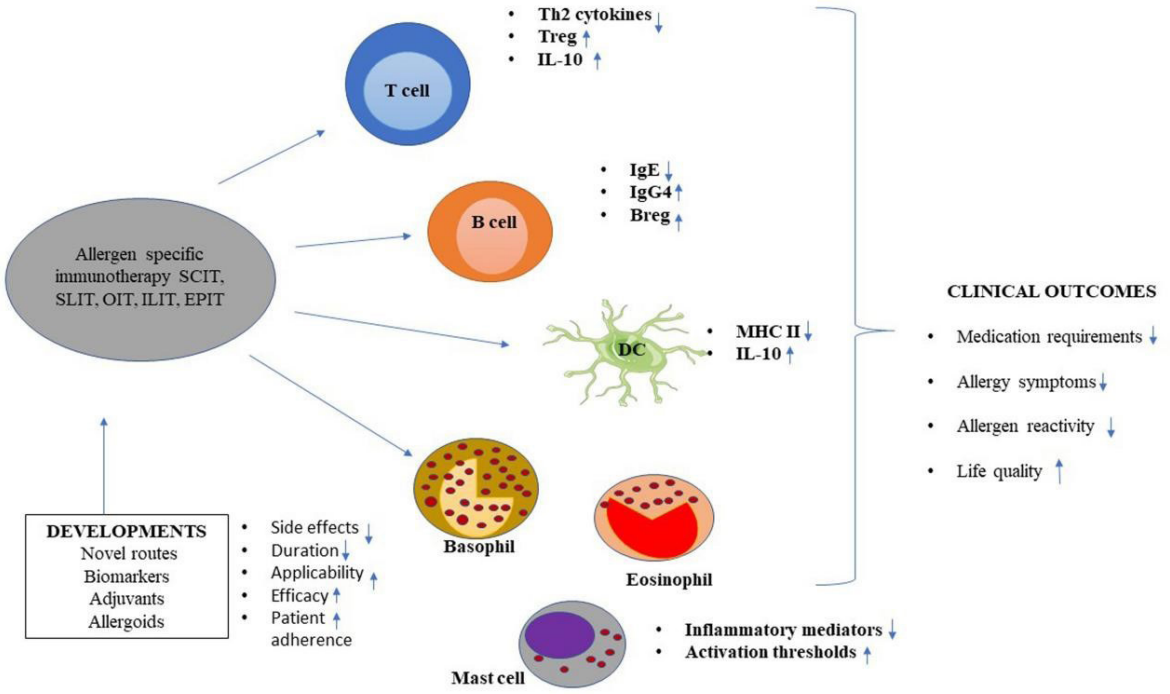

Figure 2. Mechanism of allergen-specific immunotherapy.

suming and processing allergens. Regional dendritic cells take up an allergen, which causes regulatory T cells to be formed. These cells stop allergic reactions both directly and indirectly, as depicted in **Figure 2**[10,11].

3. Routes for allergen-specific immunotherapy

Allergen-specific immunotherapy is generally provided through lymphatic, sublingual, subcutaneous, and oral routes.

3.1 Intralymphatic route

The idea is straightforward since an immune response depends on the interaction between three essential immune cells (antigen-presenting dendritic cells, B and T cells). An immune response is more likely to happen in lymphoid organs like lymph nodes, where these three immune cell types are found in high concentrations. One major aspect of why a lymph node is such an immunogenic environment is the high possibility that an antigen will bind a particular T or B cell, which is orders of magnitude higher than with peripherally delivered antigens. By contrast, the immune system largely disregards antigens outside of these organs. Several preclinical and clinical studies have shown the efficacy of intralymphatic administration of peptides, proteins, DNA, RNA, bacteria, viruses, and DCs, and the results so obtained have also been documented. Freiberger *et al*. discovered the major subclass of immunoglobulin to be IgG4 in human sera following intralymphatic immunotherapy (ILIT), while only minimal quantities of IgG1, IgG2, and IgG3 are produced. A correlation between this significant IgG4 induction and the allergen-specific T cell response generating IL-10 has also been demonstrated. Additional research has verified that ILIT-induced early allergen-specific activation of T cells has been followed by allergen insensitivity to the T cell, as seen by an increase in forkhead box P3 (FOXP3) expressing IL-10-producing Treg cells that are specific to the allergen[12–14].

As depicted in **Figure 3**, in the intralymphatic route of administration, an A naïve B cell enters the lymph node through an afferent lymphatic channel, where it then undergoes clonal growth and somatic hypermutation. Follicular dendritic cells phagocytose allergens injected into the lymph nodes, and their peptides are then given to B lymphocytes via (MHC) major histocompatibility complex molecules in the light zone of the germinal center (class II). Plasmablasts, plasma cells, and memory B cells are produced when these activated B cells proliferate and undergo differentiation. The medulla and efferent lymphatic vessels are subsequently used to leave the lymph nodes. IgG4, IgE, or other isotypes that are specific to allergens may be secreted by circulating B cells, either with or without enhanced affinity[15].

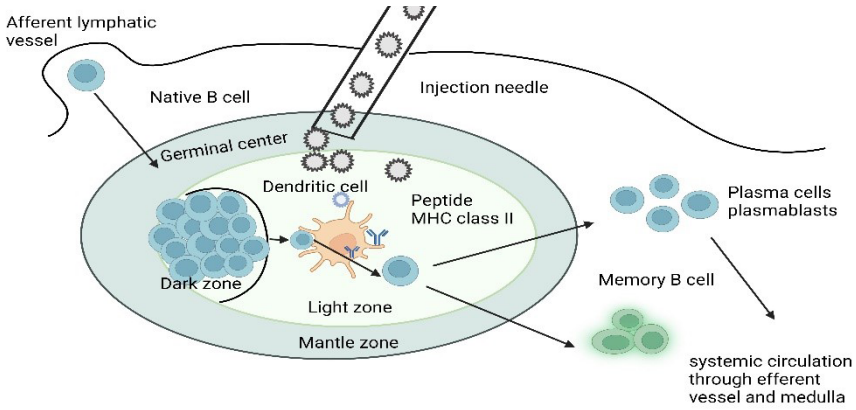

Figure 3. Mechanism of the intralymphatic route of administration of allergen for allergen-specific immunotherapy.

3.2 Sublingual immunotherapy

In sublingual immunotherapy (SLIT), allergens are given daily as drops or tablets beneath the tongue[16]. During SLIT, dendritic cells collect allergens through the oral mucosa and travel to the adjacent draining lymph nodes with a specialized microenvironment that encourages mucosal tolerance formation via the IgG antibodies generation and regulatory T cells stimulation. With a dose-related decrease in concurrent drug use, SLIT with house dust mite tablets is more efficacious for chronic allergic rhinoconjunctivitis than any first-line pharmaceutical[17]. For seasonal allergic conjunctivitis, the five-grass SLIT outperforms all pharmacology treatments, and grass SLIT is nearly as effectual as intranasal corticosteroids and more effectual as compared to other pharmacotherapies[18].

Sublingual immunotherapy (SLIT) can be administered orally and sublingually, kept beneath the tongue for a minute, and later swallowed. More data support the application of SLIT tablets than drops, especially in the case of dust mites[19]. The therapy can be practiced continually as well as in the early phase of the pollen season, starting ideally four months earlier. The standard way to start SLIT therapy is with a rapid or full dose inflation schedule. The patient can self-administer the medication at home daily. Adverse events associated with SLIT tablets are throat irritation, mouth edema, and glossodynia[20].

3.3 Subcutaneous immunotherapy

For the treatment of IgE-mediated allergy, the technique of administering repeated doses of a specific relevant allergen is known as subcutaneous immunotherapy[21]. The typical subcutaneous immunotherapy (SCIT) regimen, which uses unaltered allergen extracts, involves weekly subcutaneous injections to build up the dose, followed by maintenance doses spaced 4 to 8 weeks apart. The use of modified allergenic extracts (such as allergoids) and/or adjuvants can result in fewer accumulation doses[22].

The differences between the two types of allergen-specific immunotherapy, SLIT, and SCIT, as described above, have been depicted in **Table 1**.

3.4 Oral immunotherapy

Oral immunotherapy (OIT) is an additional SCIT substitute. Following the initial OIT reports, this strategy has been explored for sources of respiratory allergens but proved unsuccessful. Since positive outcomes have only been noticed with extracts of respiratory encapsulated allergen, it seems that the allergen easily digested in GIT will not be beneficial for OIT, such as most allergens of the respiratory part[27]. Therefore, there is no surprising particular OIT is used almost exclusively for sources of food allergens, such as milk, egg, peanuts, and to lesser extent wheat, whereas it is not utilized at all for other allergen sources[28]. Clinical OIT studies show that the development of allergen-specific antibodies, which can limit interaction between allergens and IgE comparable to SCIT, is linked to positive outcomes[29]. OIT has also been noted to affect cellular immunological reflexes, so may result in oral tolerance. Although having demonstrated clinical virtue, this will cause serious adverse events, and now on the market mainly one registered OIT vaccine accessible that is thoroughly examined in clinical research. Regarding this, the latest report reviewing OIT against peanut allergy has been reported[30].

Table 1. Differences between SCIT and SLIT

Attributes	SCIT	SLIT	References
Benefits	Symptoms improve instantly. Diminished requirement for ransom medication. Decreased risk of development from ARC to respiratory asthma. Benefits greater than single-drug pharmacotherapy.	Symptom scores improve. Less need for concomitant pharmacotherapy. After the first dose will be able to dose at home.	[23]
Recommendation	Patients who have ARC symptoms for an extended period each year are resistant to pharmacotherapies.	A high dose is recommended.	[24]
Expenditure	The expense of allergen extracts SCIT treatment. The cost of allergen extracts SCIT therapy.	Expenditure effective. Expenditure data of SLIT versus SCIT is variable.	[25]
Risks/cons	Uneasiness due to usual clinic visits. Potential for anaphylaxis and systemic reactions. SCIT has more risk of a systemic reaction than SLIT.	Less harm. An important reminder to administer doses daily at home. Rare systemic events. Safer than SCIT.	
Immune mechanism	**Demonstration**	**Demonstration**	
a) Selective apoptosis of CD27 allergen-specific T cells.	X		[26]
b) Inhibition of facilitated antigen presentation.	X		[26]
c) Increase in allergen-specific IgA and IgG4.	X	X	[26]

4. Recent advancements used in allergen-specific immunotherapy

To address the aforementioned issues, several approaches have been implemented. These include the use of (i) nanoparticles, (ii) B and T cell peptides, (iii) virus-coupled allergens, (iv) genetically modified hypoallergenic allergen derivatives, and (v) adjuvants.

4.1 Nanoparticles

For the treatment of allergic disorders, ASIT which aims to induce antigen-specific immunological tolerance is frequently utilized. However, this method necessitates using soluble antigens at high dosages for extended periods, which carries a substantial risk of adverse responses, especially in individuals who are already highly sensitized. Therefore, the advancement of allergy treatment depends on the creation of safer, more effective techniques for this approach[31]. Due to the following factors, encapsulating allergens within nanoparticles (NPs) may be one method for improving AIT: nanoparticles may act as a vehicle for carrying DNA molecules, peptides, and proteins as well as having adjuvant properties[32]. Encapsulation or surface coating of the cargo are the two alternative modes of transportation. Encapsulation provides defense against acidic or enzymatic degradation, distribution, and co-delivery of other molecules to the desired site of action, permitting high local concentrations and preventing immune system identification of the cargo molecule[33]. When an allergen is shielded during the ASIT therapy, IgE linked to a mast cell or basophil surface is unable to recognize it, which should lessen or even eliminate negative effects. On the other hand, allergen-coated NPs enable IgE cross-linking on the surface and subsequently activate immune cells; they are typically utilized for studies on prophylactic allergen vaccinations in mice.

Utilizing various delivery methods which can intensify the allergen in the target organs, tissues, or cells can reduce the allergen quantity required for the treatment and, as a result, lower the probability of unfavorable feedback[34]. These conveyance systems are often made of nanomaterials and biomaterials, and their features can be adjusted with each application based on the type of cargo being delivered, the target cells, and the route of administration[35]. In addition, based on their physicochemical characteristics, these materials have a direct effect on allergic response (negatively or positively) outside the necessity of therapeutic cargo, therefore

some can be used as straight in allergy as a therapeutic option[36].

To treat allergic illnesses, bio-, and nanomaterials can be employed in three different ways[37,38]:

- Making use of bio- and nanomaterials that have an immediate impact on the cells responsible for the allergic reaction.
- Bio- and nanomaterials are used as delivery systems for allergens in immunotherapy.
- Bio- and nano-materials are used as co-delivery methods for immunomodulatory and allergen compounds.

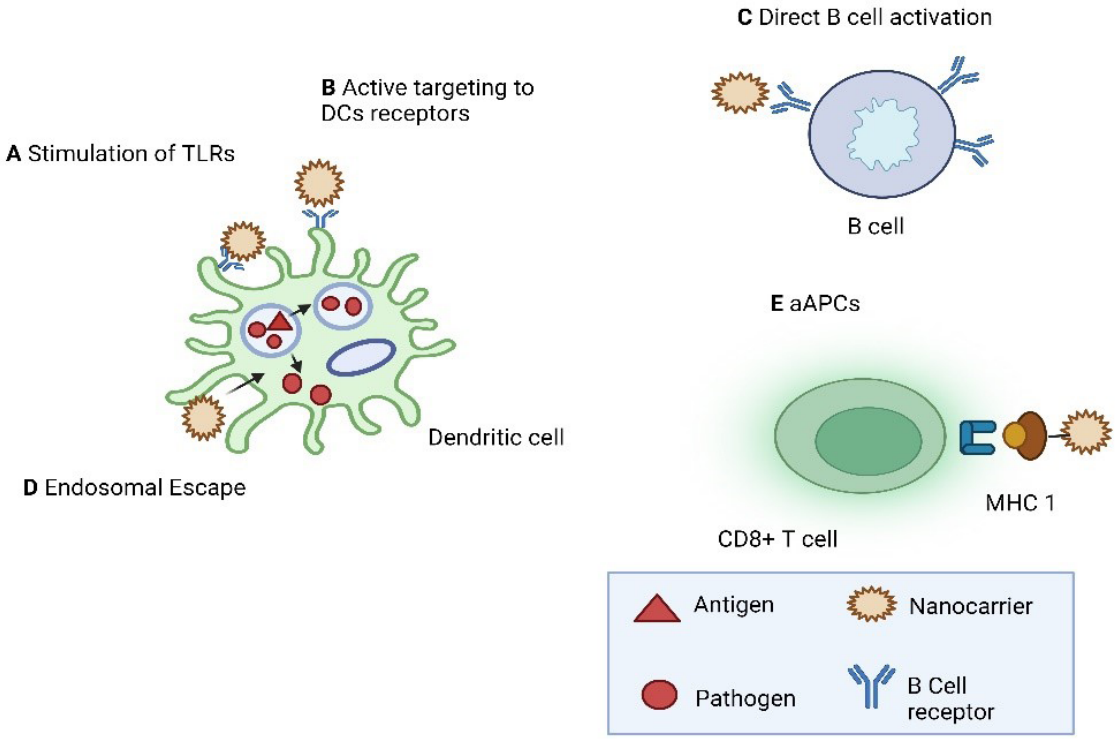

Figure 4. Nanotechnology-based approaches for modification of immune responses.

Figure 4 illustrates the following:

a) TLR (Toll-like receptor) agonists may be supplied using nanocarriers and activate endosomal or surface receptors to cause cellular or humoral responses, respectively.

b) These cells can be activated by coating nanocarriers with antibodies that target certain dendritic cell (DC) receptors, such as CD40.

c) Direct stimulation of B cells can increase their activity, which will support the creation of antibodies and humoral responses.

d) Cellular responses are favored by nanocarriers with traits that encourage antigen endosomal escape.

e) Direct stimulation of CD8+T cells using artificial antigen-presenting cells stimulates cytotoxic T lymphocytes (APCs).

4.1.1 Categories of nanomaterials/nanoparticles applied in allergen immunotherapy

4.1.1.1 Polyesters

Polyesters are a class of compounds that have already received US Food and Drug Administration approval due to their well-documented safety, biodegradability, and biocompatibility in human usage (FDA). The main application of polyglutamic acid (PGA) and PLGA are biodegradable polymer (synthetic) nanocarriers. To change the antigenicity of the nested antigens and improve distribution through various administration routes, it is supposable to alter their surface characteristics, size, and release profile (rate of biodegradation)[39].

4.1.1.2 Polysaccharide polymers and carbohydrate-based particles

The easy-to-produce polymers obtained from

natural sources known as polysaccharides are another molecular class that has been researched in this context. On this subject, chitosan is a naturally occurring polymer that is generated by shrimp which is highly plentiful. It has various beneficial qualities, including low-cost production, biocompatible, biodegradable, and lack of adversity[40]. It has previously received approval for human usage in the US and Europe as a natural, nontoxic polysaccharide for dressing and other hemostatic treatments. Notedly, chitosan might offer a charge (cationic) that might assist as an adjuvant to works via encouraging the development of DCs for use in the field of immunomodulatory drugs. The mucoadhesive ness of chitosan is another significant characteristic that builds it markedly appealing for fostering the immunity of mucosal tissue. To improve vaccination against allergy, other carbohydrate-based polymers (like beads of sepharose) have been proposed as a new particulate adjuvant[41].

4.1.1.3 Protamine-based nanoparticles

Protamine is a biodegradable, 4 kDa peptide, high in arginine that has been employed in human medicine for many years. Electrostatic interaction can be used to create protamine NPs that are entangled with RNA or DNA oligonucleotides and exhibit the best biocompatibility and stability[42]. Additionally, these nanoparticles can effortlessly transfer payload within the nucleus because protamine contains a nuclear localization signal, which boosts the effectiveness of targeted gene therapy[43].

4.1.2 Liposomes

The dual chemical nature of liposomes, which are globular vesicles made of more than one lipid bilayer phase enclosing anhydrous compartments, enables the transfer of both hydrophilic and hydrophobic compounds. Nanosized liposomes offer a wide range of uses as medication and gene carriers due to their exceptional biocompatibility and biodegradability[44]. Protein allergens could be chemically conjugated to the liposome's outer surface or encapsulated within the lipid lumen bilayer[45]. The possibility of improving the protein cargo's solubility and bioavailability and also its *in vivo* performance, to safeguard it from unwanted contacts with other molecules or cells and maximize the positioning of a medication's site of action, are the main benefits of their utilization in drug administration.

4.2 Hypoallergenic derivatives

To minimize IgE-mediated adverse effects during SIT, multiple researchers have created recombinant hypoallergenic allergen variants that are distinguished through decreased IgE activity but retained epitopes of T cell[46]. These molecules are created using a variety of t-DNA recombinant technologies, such as fragmentation or mutation to decrease IgE activity and maintain the frequency band of the original wild-type allergens' T cell epitopes[47]. The variants of Bet v 1, the main birch pollen allergen, have been used in the first recombinant allergen immunotherapy trial eleven years ago. The intervention of allergen-specific obstructive IgG antibodies has been discovered to be a key underlying process by using recombinant hypoallergenic allergen derivatives[48]. Recently, several recombinant hypo allergens have been developed and characterized in *in vitro* and experimental animal models for the therapy of birch pollen, cat, and dust mites. They have been created using a variety of techniques, including mutations to boost IgG response, epitope insertion to cause modified fold, reassembly of sequence elements, and oligomerization to raise IgG responses[49].

The ability to dependably manufacture recombinant allergens in large quantities and with specific protein concentrations is one of their main benefits. Recombinant allergens have the potential benefit of increasing the safety and effectiveness of allergy immunotherapy without sacrificing immunogenicity, in addition to consistency and quantity[9].

Figure 5 describes the steps for the creation of a recombinant cDNA, as depicted below[50]:

(A) Elucidation of the proteins' amino acid sequences (allergens) that induce allergic reactions,

(B) Extraction of messenger RNA from the genetic code,

(C) cDNA sequence insertion into the genetic code of bacteria (Escherichia coli),

(D) Recombinant cDNA polymerization, and

(E) Evaluation in research of clinical immunology.

4.2.1 Allergen-specific immunotherapy using first-generation recombinant hypoallergenic derivatives

The first-generation recombinant hypoallergenic derivatives share the property which, upon

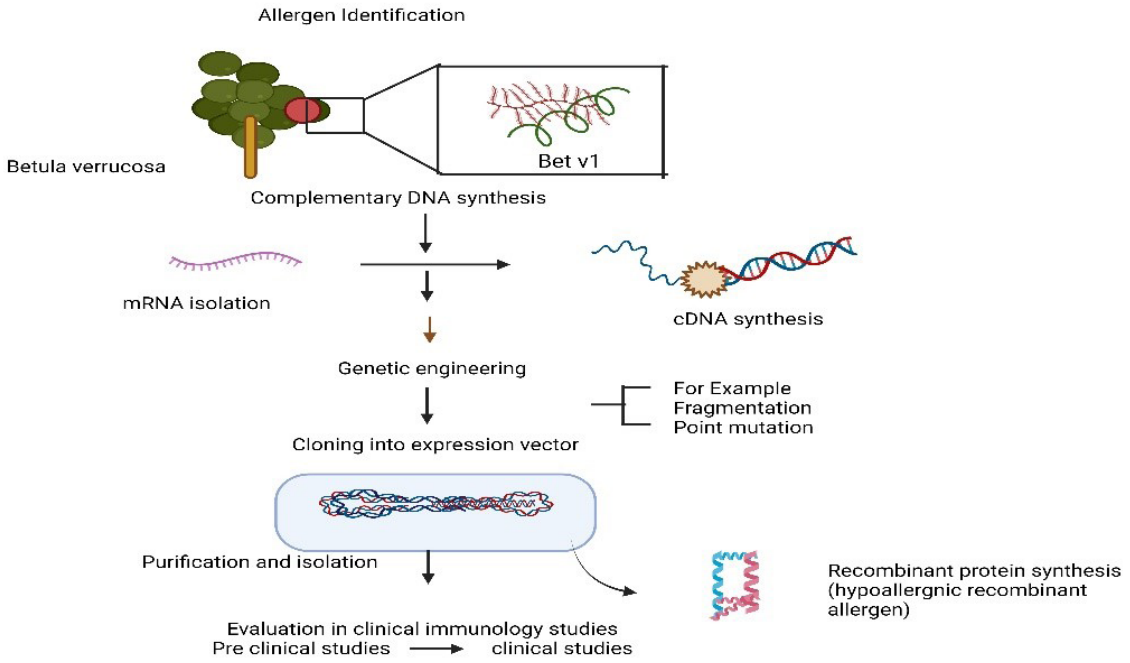

Figure 5. Method for creating recombinant allergens.

immunization, causes the patient to produce allergen-specific IgG responses that battle for binding with IgE and, based upon specificities and titers of the blocking IgG response, mitigate and basophil degranulation mediated by IgE, and therefore IgE facilitated allergen presentation as well as immediate allergic symptoms and thus activation of T cell and late-phase allergology[50]. Therapies also may lower allergen-specific IgE levels by reducing antigen-specific IgE synthesis, which is increased by allergen exposure. According to studies looking into the mechanisms underlying, allergen derivatives that are non-IgE-reactive with epitopes of T cell can cause late-phase allergic inflammation that is not mediated by IgE but MHC-dependent and T cell-dependent[51,52].

4.2.2 Allergen-specific immunotherapy using second-generation recombinant hypoallergenic

These derivatives depend on peptides of 20–40 amino acids in length that are hypoallergenic and/or nonallergenic, obtained by allergen IgE binding sites, as well as through integrating to permeable non-allergenic carrier protein made immunogenic[53]. Formerly, such a strategy has been proposed as one option for establishing hypoallergenic AIT vaccines along with showing that it is possible to chemically covalently couple non-allergenic allergen peptides to carriers like keyhole limpet hemocyanin to produce a vaccine that will arouse allergen-specific IgG antibodies upon immunization blocking allergic patients IgE binding to the allergen and blocking allergen binding basophil activation via IgE[54]. BM32 vaccine for grass pollen allergy, which is made up of four recombinant fusion proteins, along with PreS from the hepatitis B virus integrated to nonallergenic peptides of grass pollen allergens, has a brilliant security profile, has excellent clinical efficacy and with a few injections generates allergen-specific blocking IgG responses.

In clinical studies using hypoallergenic allergen derivatives which are non-IgE-reactive, it has been discovered that T cell epitopes that are derived by allergen can cause non-IgE-mediated or late side effects[55]. Thus, a novel class of allergy vaccines has been created to reduce IgE and T cell-mediated adverse effects. This approach depends on the identification of allergen peptides that serve as main IgE binding sites for allergens but lack allergenic action on their own[56]. These peptides can be chemically linked to a carrier protein or produced as recombinant fusion proteins with a carrier protein. They generally range in length from 20–35 amino acids[57]. With the use of the carrier protein and T cells, immunization with these carrier-bound allergen peptides produces IgG antibodies against IgE epitopes on allergens and does not actuate al-

lergen-specific T cells. Since these vaccines contain fewer allergen-specific T cell epitopes, they should avoid T cell-mediated adverse effects[58]. In addition to providing immunity against allergens and immunomodulation, virus transporter proteins have been proposed to promote positive antiviral immunity. A similar approach that uses an allergen tries to produce IgG antibodies that are specific to that allergen[59].

4.3 Immunoregulatory T cell epitope peptide

As entire allergen extracts are employed, specific immunotherapy has its limitations. Applying short synthetic T cell peptides is a novel, therapeutic strategy that shows promise. These synthetic peptides contain immunoregulatory epitopes (SPIREs) that range in size from 13 to 17 amino acids[60]. With the first evidence that synthetic T cell tolerating peptides might establish tolerance and so offer a treatment option for IgE-dependent diseases, the idea of applying them in the context of specific immunotherapy was first suggested in the mid-1990[61]. These first-generation peptides, which are lengthier in terms of the number of peptides >30, have a profile of events with a late onset. Additionally, the therapeutic outcomes aren't any better than those of traditional subcutaneous immunotherapy[62]. Consequently, the continued development of this strategy has been put on hold in the 1990s.

The peptides' short length eliminates any chance of activation of inflammatory cells or IgE-cross-linking, and attentive dose titration appears to prevent delayed asthma reaction that has been previously shown with the longer peptides[63] (benefit of peptides from the second generation).

This brand-new artificial peptide immuno-regulatory epitope (SPIRE) has been created to induce tolerance by attaching to MHC class II molecules on antigen-presenting cells and activating regulatory T cells as a result[64]. The two pathways that underlie traditional AIT that have been most commonly documented are increased IL-10 production and Tregare induction. Similar to this, higher IL-10 production during treatment is linked to the success of antigen peptide therapy, such as initial bee venom investigations and SPIRE therapy[65]. This suggests a function for Treg. As per the research reports, in an allergen peptide therapy conducted on a cat model during clinical research, IL-10 is mandatory for the silencing of peptide-induced allergen-specific immune response and an antigen-specific CD4+ T cell induction with regulative function[66]. Analysis of skin from allergen challenge areas after peptide therapy has revealed an increase in CD25+ cells and CD4+IFN-c+, implying roles for immunological variation and T cell regulation[67]. It ought to be that the overlap between Treg and Teff surface marker expressions, particularly when stimulated, makes many studies of Treg subsets and function, particularly those using clinical data, difficult to understand. To differentiate between activated CD4+ T cells and naturally occurring or artificially produced Treg, addition, operative investigation, and phenotyping of tissue T cells and peripheral blood are necessary. With effective peptide immunotherapy, there is a minimal indication that a particular IgG4-blocking antibody is induced. Since peptides utilized for AIT, especially SPIRE, are pithy and scanned for the scarcity of IgE binding and capacity to activate inflammatory cells, they are unlikely to stimulate the development of antibodies[68–72].

4.4 Virus-like particle-coupled allergens

Virus-like particles (VLPs) are multimeric entities made up of viral capsid-forming proteins that share the native virus's shape but are devoid of genomic material[73]. As a result, they cannot reproduce, ruling out the possibility of the occurrence of reversion mutations or pathogenic infections. Virus-like particles (VLPs) can be spherical, filamentous, or enclosed, and their sizes can range from 20 to 200 nm[74–76].

Normally, harmless chemicals that induce TH2 cytokines and IgE antibodies, which result in the degranulation of basophils and mast cells, are what cause allergic inflammation[77]. Several initiatives use VLP-based immunization strategies to treat allergic inflammation. Preclinical information on a peanut allergy vaccine candidate has been provided by Matthew Heath in 2018 (Allergy Therapeutics, Worthing, UK). Ara h 1 or Ara h 2 are vital peanut allergens that have been linked with cucumber mosaic virus (CuMV) particles. The CuMV-Ara h 1 vaccine has been reported to completely protect mice with peanut extract challenge in a mouse model of peanut allergy. It's interesting that in mice with

peanut extract sensitization, the vaccinations have not caused anaphylaxis[78].

4.4.1 The 2Ds in virus-like particle based-vaccines: "Design" and "delivery"

4.4.1.1 Design

Design as well as delivery, sometimes known as the 2Ds of vaccinology, are two essential elements for the effective production of a safeguard vaccine[79]. The best design permits the repeated presentation of native antigens on TLR ligand-loaded VLPs, which directly stimulates B cells to produce IgA and IgG and also polishes up T cell responses[80]. Causation of mucosal responses or permissive dosage sparing as well as arbitrating direct oncolytic activity, if given to the tumor, may depend on effective transport. Higher definite antibody responses, powerful T cell responses, and optimal clinical efficacy are the intended outcomes of ideally created and administered vaccinations, which will produce excellent dynamic immune responses[81].

4.4.1.2 Delivery route

Clinical trials have demonstrated that the administration method has a remarkable influence on the effectiveness of VLPs[82]. The majority of FDA-approved vaccines are applied subcutaneously or intramuscularly. However, compared to other immunization methods, Cubas *et al*. showed that intradermal administration of VLPs significantly boosted antibody synthesis and antigen-specific T cell responses[83]. The lymphatic vessels' 200 nm holes allow for the diffusion of small particles. So VLPs with an average size of 30 nm can therefore effectively move from the injection site to the draining lymph nodes via draining into the lymphatic system[84].

4.4.2 Key properties of VLPs favoring their immunogenicity

The increased immunogenicity of VLPs compared to soluble antigens can be explained by several immunological and physicochemical factors[85].

(A) Effective antigen-presenting cell uptake,

(B) Direct lymph node trafficking,

(C) Innate immune signaling stimulation,

(D) Interactions with B cell antigen receptor (BCR) for powerful antibody response,

(E) Production of autoantibodies as a result of the high-density presentation of self-antigens on the VLP surface.

4.5 Adjuvants in ASIT

A substance known as an adjuvant helps to improve immune responses via physical or chemically collaborate with antigens[86]. First-generation adjuvants include aluminum, calcium phosphate, and microcrystalline tyrosine, whereas second-generation adjuvants include Toll-like receptors (TLR)[87]. Adjuvant-containing formulations could improve the protective allergen-specific responses in AIT while lowering the antigen dose and frequency of administration, hence reducing adverse effects[88]. They exert their effect by altering innate immunity, increasing APC capture, and a variety of other processes, such as the formation of a depot at the injection site.

A great adjuvant should activate the innate immune system when combined with an allergy vaccination to increase the body's reaction to the antigen. The most widely used adjuvants that are permitted for use in AIT in Europe and the US are aluminum salts (alum). Merits and demerits of some adjuvants of ASIT are listed in **Table 2**.

4.5.1 Alum

A large percentage of subcutaneous immunotherapy formulations in Europe today use alum, one of the oldest and most widely used types of adjuvant in modern vaccinations. Initially, it has been thought that alum solely has immunomodulatory effects affecting the depository formation. Antigens are largely absorbed onto the surface of alum by static interactions (OH groups) at pH values slightly below the isoelectric points of the necessary proteins for adsorption[89]. Due to their poor solubility, larger aggregates of particulate matter in the micrometer size range arise in the adjacent lymphatic organs and tissue. Because of the quick chelation with alpha-hydroxycarboxylic acid in the interstitial fluid, the adsorbed antigens release over a longer length of time. The APCs go on to further engulf the released antigens, take them up into the cells, digest them proteolytically, and present them for the powerful immune response[90]. Alum exhibits a better safety profile than non-adjuvant subcutaneous im-

Table 2. Merits and demerits of some adjuvants of ASIT

Adjuvant	Merits	Demerits	References
Alum	Vaccines have a wide range of applications.	Non-biodegradable Th2 immune responses are induced.	[89]
Microcrystalline Tyrosine	better systemic and local tolerance.	Not recommended for people who have a tyrosine metabolic disorder.	[95]
Calcium phosphate	Biocompatible and Biodegradable.	Adjuvant activity is lower as compared to alum.	[93]
CpG-ODN	Th2 bias can be overcome by co-administration with another adjuvant.	DNase degradation and a short half-life.	[96]

munotherapy because it deposits the allergen locally and slows down the spread to the bloodstream[91,92].

4.5.2 Calcium phosphate

Calcium phosphate (CaP) has been created as an adjuvant forty years ago. It is used in vaccines for several contagious illnesses, including diphtheria, poliomyelitis, and tetanus. When used as a booster dose for the diphtheria vaccination, it is both more effective than alum and to be well tolerated in individuals[93]. In AIT CaP works through a depot effect and gradually releases the allergen, among other mechanisms. Additionally, the uptake of allergens by phagocytic cells (such as monocytes, macrophages, and DCs) is made easier by the allergen adsorption onto CaP microcrystals as particles, increasing the immunogenicity of protein allergens and inducing potent IgG responses as well. As a mineral adjuvant, CaP also releases the pro-inflammatory mediators IL-1 and IL-18 through NALP3 inflammasome activation[94].

4.5.3 Microcrystalline Tyrosine

The non-essential, biodegradable L-Tyrosine amino acid, which has a half-life of 48 hours at the injection site, is present in Microcrystalline Tyrosine (MCT) in a crystalline form, developing as a depot for immunomodulation using allergens, entire cells, lipids, and polysaccharides for controllable release from the site of injection. Broad vaccination scope with characterized adsorption capacity and durability that supports Th1-specific immunological enhancement MCT is a unique crystalline depot adjuvant formulation and it produced in mice responses from the B and T cells that were largely comparable. Compared to alum, MCT generated less Th2 polarisation (less IIL-4 and IgE). It is significant to note that preclinical models consistently demonstrate protective effectiveness when MCT is combined with less immunogenic antigens, such as ovalbumin. MCT was discovered to have a capacity for high protein binding[95].

4.5.4 CpG-oligonucleotides

Through a variety of cell types and molecular pathways, CpG-oligonucleotides (CpG-ODNs), when given under the right circumstances, causes immunological tolerance. To improve the therapeutic effects of AIT formulations and get around the problems described above, such as adverse consequences and demanding treatment regimens, CpG-ODN is added. Indeed, through a variety of immunological mechanisms, CpG-ODN has demonstrated the potential to lessen allergic disorder's burden. According to numerous lines of research, CpG-ODN primarily modulates the immune system through two complementary processes. On the one hand, the production of tolerogenic DCs, Breg, and Treg cells are part of an immune regulatory response. However, specific IgE (sIgE) is prevented from adhering to allergens by the formation of allergen-specific neutralizing antibodies, which reduces the number of allergy-effector cells such as eosinophils, basophils, or mast cells. The features of CpG-immune-modulatory ODN might eventually promote clinical and immunological tolerance to the allergen[96,97].

5. Comprehensive care pathways for ASIT

Immunologists and allergists are essential in identifying and treating AR patients. Clinicians may adopt a growing number of technologies to improve treatment for AR patients, including social media outreach, mobile applications, and telemedicine. Given the high rate of untreated patients, it is critical to acknowledge the future management of AR by healthcare colleagues including pharmacists and primary care physicians. Additionally, establishing multidisciplinary care clinics in cooperation with other authoritative medical specialists may enhance overall treatment for individuals with AR[98].

5.1 The world wide web

Relationships on social media among doctors and patients have proved to encourage healthy behavior and attitude in patients, emphasizing a potential opportunity for doctors. In a poll of patients who have used the Internet, 53% looked up allergy information before a consultation, and 47% looked up allergy information afterward. Furthermore, there is proof that social media has been shown to enhance clinician perception and made it easier to use fresh study findings in clinical practice. The future of AR treatment will likely be shaped by the growth of immunologists' social media presence, which will provide trustworthy medical information on new developments in the area and, if successful, enhance patient care[99,100].

5.2 Telemedicine

The Centers for Medicare and Medicaid Services (CMS) defines telemedicine as "the exchange of medical information from one site to another via electronic communication to improve a patient's health"[101]. Telemedicine is not a novel concept, but it has received attention as a consequence of the coronavirus illness crisis in 2019. Before the pandemic, reports indicated that e-consults increased from 1% to 10% of all new consults between 2016 and 2018[102]. A recent study of telemedicine in allergy and immunology conducted between April and May 2020, has found that 77 percent of patients who have experienced e-visits are comparable to an in-person visit and that almost 97 percent of these patients have truly been happy with their experiences. Following pediatric e-consults, parents have been found to express similar feelings, with 56% preferring telemedicine visits over in-person consults in the future. Telemedicine offers patients numerous advantages, including reduced travel costs, as well as increased access to specialized treatment for people residing in underserved urban or rural locations[103].

5.3 Personalized medicine

Precision medicine, or giving the right treatment to the right patient at the right dose at the right time, necessitates accurate diagnosis and monitoring. Even though allergology has been using precision medicine for more than a century, it presently refers to the process of using modern "omics" technology to find biomarkers or genes to determine if a treatment is beneficial. Advanced bioinformatics is utilized to understand and query the datasets using artificial intelligence, and platform the approaches in genomes (by far the most resilient), proteomics, transcriptomics, metabolomics, lipidomics, and microbiomics to build enormous global databases. This kind of population-based dataset analysis can deliver innovative information that can be used to choose the best treatment option from a larger pool of specific biologicals. A growing proportion of people have inborn errors of immunity (IEI), which can be selectively addressed with therapies. The massive datasets generated by time of flight mass cytometry (CyTOF), basophil activation tests, next-generation gene sequencing, and RNA sequencing have enabled successful research. This kind of population-based dataset analysis can deliver innovative information that can be used to choose the best treatment option from a larger pool of specific biologicals. A growing proportion of people have inborn errors of immunity (IEI), which can be selectively addressed with therapies. Research is made possible by the enormous datasets produced by microarrays, time of flight mass cytometry (CyTOF), basophil activation assays, next-generation gene sequencing, and RNA sequencing. The likelihood of tiny populations of highly dangerous cells being hidden by many signals of more frequent or active cells is decreased via the development of better single B and T cell immunophenotyping employing flow cytometry-based assays. This makes it possible to longitudinally profile immune responses in patients before and after AIT using appropriate cell subsets[104–106].

6. Future perspective

The development of ASIT may yet offer significant benefits to patients with allergic diseases, although it has been used successfully for more than a century. When it comes to allergen immunotherapy, perspectives on accurate diagnoses and tactics include less expensive treatments with greater effectiveness and shorter treatment periods, but earlier diagnosis as well. The treatment of allergic diseases with ASIT begins in childhood, including the treatment of atopic dermatitis in children possibly tested for its ability to avoid allergic comorbidity patterns[107].

Current ASIT-based approaches for treating allergy illnesses concentrate on several different factors, contributing to the following:

I. Prevention approach: preventing the progression of rhinitis to asthma and from mono- to multi-sensitization;
II. Strategy for identifying the patients who will get benefit from ASIT by the discovery of the appropriate biomarkers;
III. Strategy to increase the tolerance and safety of treatment regimens, which can be addressed through purification and the use of recombinant allergens;
IV. Improved treatment formulation can be achieved by using carriers, such as liposomal depots encapsulating allergens, and supplied with or without adjuvants, or by targeting the antigen with glycated products, using an adjuvant like VitD3, or by improving antigen targeting[108].

As a result, there is a clear need to build ASIT for the aforementioned manifestations, first and foremost to be capable of combating various allergic symptoms with impactful ASIT vaccines and, more importantly, to investigate the use of ASIT for the prophylactic measures. Only molecular approaches, not allergen extract-based approaches, are accepted to be used to further develop ASIT systematically.

7. Conclusion

The ASIT is the only disease-modifying medication available for allergic people. The key question in innovative allergy treatment strategies is how to maintain and regain tolerance. Allergen Specific Immunotherapy (ASIT) has evolved in numerous manners, and partial tolerance can be restored. The induction of allergen-specific regulatory subsets of T and B cells is the driving mechanism behind such therapeutic strategies. There is still a need for more studies on patient safety in cases of severe responses and limited effectiveness for specific allergens. Nanomaterial-based therapeutic strategies, recombinant technology, and probiotics hold great promise for future development. The adjuvant allergen formulation with immunomodulators may contribute as a promising solution for the treatment of allergies. The allergy can be managed by several integrated pathways also such as telemedicine, personalized medicine, and other social media tools, and these tools play a major role in the holistic care for allergic patients.

Conflict of interest

The authors declare no conflict of interest.

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