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REVIEW

Development of a peptide conjugate vaccine for inducing therapeutic anti-IgE antibodies

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ABSTRACT

Introduction: Given the multifaceted effector functions of IgE in immediate hypersensitivity, late-phase reactions, regulation of IgE receptor expression and immune modulation, IgE antibodies have long represented an attractive target for therapeutic agents in asthma and other allergic diseases. Effective pharmacologic blockade of the binding of IgE to its receptors has become one of most innovative therapeutic strategies in the field of allergic diseases in the last 10 years.

Areas covered: The latest strategies targeting IgE include the development of a therapeutic vaccine, able to trigger our own immune systems to produce therapeutic anti-IgE antibodies, potentially providing a further step forward in the treatment of allergic diseases. The aim of this review is to discuss the discovery strategy, preclinical and early clinical development of a peptide conjugate vaccine for inducing therapeutic anti-IgE antibodies.

Expert opinion: Outside the area of development of humanized anti-IgE monoclonal antibodies, the research field of therapeutic IgE-targeted vaccines holds potential benefits for the treatment of allergic diseases. However, most of the experimental observations in animal models have not yet been translated into new treatments and evidence of human efficacy and safety of this new therapeutic strategy are still lacking.

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1. Introduction

After 50 years since the discovery of immunoglobulin E (IgE), substantial advances have been made in understanding the immunological pathways of allergy, the chemical mediators involved, and the immune responses that regulate its expression. IgE has been defined as the fifth class of antibodies, capable of transferring sensitivity to allergens [1,2]; it is now clear that, in addition to mediating the classic immediate hypersensitivity reactions by inducing acute mediator release by mast cells, IgE has a number of immunomodulatory functions [3,4]. Biological functions of IgE are mediated by their interactions with two structurally different receptors, FcεRI and CD23, high- and low-affinity receptor respectively, each present on a broad range of immune effector cells [3,4]. Effective pharmacologic blockade of the binding of IgE to its receptors has become one of most innovative therapeutic strategies in the field of allergic diseases in the last 10 years. Innovative technologies in molecular biology and immunogenetics have contributed to the development of selective anti-IgE-blocking agents [5,6]. Omalizumab, a recombinant DNA-derived humanized monoclonal antibody (mAb) that targets circulating free IgE, is the first biological therapy approved for the treatment of allergic asthma and chronic spontaneous urticaria (CSU) [7]. This IgE-specific immunoglobulin G1 (IgG1) antibody exerts its immunomodulatory function of IgE-mediated inflammation through different mechanisms: by binding to the constant region (Cε3) of the

IgE molecule, omalizumab decreases levels of circulating free IgE and prevents their interaction with IgE receptors on mast cells, basophils, and other immunologic cells; by depleting IgE, omalizumab downregulates FcεRI expression on inflammatory cells; omalizumab also reduces FcεRI expression on dendritic cells, leading to a reduction in allergen presentation to T cells and a global attenuation in the Th₂-mediated allergic pathway [7]. Recent evidence also suggests a potential role of omalizumab in the modulation of innate immunity against viral pathogens and in the airway remodeling process in asthmatic patients [8,9]. Besides the development of a generation of the new anti-IgE mAbs, the latest strategies targeting IgE include the development of a therapeutic vaccine, able to trigger our own immune systems to produce therapeutic anti-IgE antibodies, potentially providing a further step forward in the treatment of allergic diseases.

2. Anti-IgE vaccine

2.1. Discovery strategy and preclinical development

The challenge of developing an effective vaccine started in 1985, when Marshall and Bell demonstrated that auto anti-IgE antibodies, which reduce IgE-mediated allergic responses, can be induced. By intraperitoneal injection of purified aluminum hydroxide (alum) precipitated rat myeloma IgE in rats, they successfully induced autoantibodies against self-IgE [10] and reduced specific IgE responses [11] and skin mast cell

Article highlights

- In addition to mediating the classic immediate hypersensitivity reactions by inducing acute mediator release by mast cells, IgE has a number of immunomodulatory functions. Thus, IgE has become a major therapeutic target for allergic diseases.
- Omalizumab, the unique currently approved IgE-specific IgG1 mAb, is a validated therapeutic tool both in adults and children, in particular for the treatment of uncontrolled allergic asthma. Current limitations of omalizumab therapy are mainly problems of high cost and patients' adherence to treatment.
- Novel investigational anti-IgE monoclonal antibodies with improved pharmacodynamic properties are in the pipeline, potentially offering alternative mechanisms of modulating IgE pathway.
- The latest strategies targeting IgE include the development of a therapeutic vaccine, able to trigger our own immune systems to produce therapeutic anti-IgE antibodies.
- A therapeutic anti-IgE vaccine may offer long-term efficacy reducing costs, increasing patients' compliance and safety and potentially modifying the course of the allergic diseases in comparison with current available biological therapy.
- To date, evidence of efficacy and safety of an anti-IgE vaccine are limited to preclinical studies, and most of the experimental observations in animal models have not yet been translated into new treatments.

This box summarizes key points contained in the article

degranulation in rats [12]. Since this discovery, vaccines targeting IgE have been further investigated (Table 1).

Chimeric IgE vaccines were obtained by fusing a large portion of rat IgE (whole Cε2 and/or Cε3) to a heterogenous carrier protein (either the glutathione-S-transferase protein or opossum Cε2 and Cε4) forming a chimeric IgE molecule or a fusion protein [13,19]. Administration of chimeric IgE vaccine in ovalbumin-sensitized rats resulted in antirat IgE antibody responses and in a 92% reduction of serum IgE [19]. Although these vaccines induced strong antiself IgE responses, the polyclonal antibodies to IgE induced by the vaccine act against all epitopes in the target Cε2 and/or Cε3 and may cross-react with other immunoglobulins containing the same epitopes.

In contrast to conventional vaccines that include large proteins and carry an unnecessary antigenic load, peptide-based vaccine represents an expanding strategy that relies

on usage of short peptide fragments to engineer the induction of highly targeted immune responses, consequently avoiding allergenic sequences [20]. Moreover, considering the specific case of anti-IgE vaccine, it is not possible to use whole IgE as the vaccine antigen, since antibodies that can bind to receptor-bound IgE could result in cross-linking and induce anaphylaxis [21]. However, peptides alone are poorly immunogenic and unable to induce the required titers and functionality of anti-peptide antibodies [20]. The use of a carrier protein to provide structural support of the correct conformation is required for adequate immunogenicity of self-peptide based vaccines and for the induction of antibodies that can cross-react to the intact targeted molecule [22].

IgE peptide-based vaccine was firstly elaborated by Stanworth et al. in 1990 [14]. This type of IgE vaccine reduces the possibility of cross-reactivity because the peptide sequences used are short and are IgE-specific. A peptide derived from human IgE Cε4 domain was synthesized and conjugated to a carrier named Keyhole Limpet Hemocyanin (KLH). The antiserum, obtained from rabbits immunized with the conjugate vaccine, was able to inhibit histamine release from rat mast cells. Moreover, immunization of sensitized rats with the conjugate reduced histamine concentrations and abolished egg white-induced anaphylactic reactions in response to egg white challenging [14].

Recently, one or more Cε3-derived peptides of various lengths were conjugated to a carrier such as KLH, surface antigen of the hepatitis B virus (HBsAg), or a purified protein derivative of tuberculin [15,23]. While most studies on anti-IgE vaccines have been conducted in rodents, IgE lowering following immunization with a peptide conjugate vaccine or a chimeric protein vaccine has also been demonstrated in dogs [23,24].

The antigenicity of either the chimeric IgE vaccine or the IgE peptide-based conjugate vaccines is not strong, requiring the addition of the adjuvant CFA/IFA (Freund's Complete Adjuvant/Incomplete Adjuvant) that cannot be used in humans to elicit anti-IgE responses [21]. In order to find an adequate carrier, virus-like particles (VLP) have been considered [25]. It has been demonstrated that administration of the VLP vaccine induced high and long-lasting immune responses

Table 1. Pivotal studies in developing anti-IgE vaccine.

Description of vaccine	Animal model/clinical trial	Results	Author, year
Alum precipitated rat myeloma IgE	Rats	Reduction of specific IgE response and skin mast cell degranulation	Marshall JS, 1985, 1987, 1989 [10–12]
Chimeric IgE vaccine	Rats	Reduction of serum IgE levels	Hellman L, 1994 [13]
IgE peptide-based vaccine conjugate to KLH	Rabbits, rats	Reduction of serum histamine concentrations and anaphylaxis reactions	Stanworth DR, 1990 [14]
IgE peptide-based VLP vaccine	Rats, mice	Sera from vaccine-immunized rats contained high titers of antibodies, which reacted with human IgE	Peng Z, 2007 [15]
Qb-VLP peptide P and peptide Y	Mice	Production of high levels of IgE-specific antibody that bound to free IgE and enhanced the rate of clearance of human IgE after a bolus injection into immunized mice	Champion BR, 2011 [16]
	Non-human primates	Reduction of serum IgE levels	Weeratna RD, 2016 [17]
	First human phase I trial	Modest lowering of serum IgE levels	Wong JY, 2016 [18]

IgE: immunoglobulin E; KLH: Keyhole Limpet Hemocyanin; QB: Q-beta bacteriophage; VLP: virus-like particles.

to the targeted self-protein even without the use of any adjuvant [26,27]. These large particles are highly antigenic because they improve the presentation of the epitopes to cells of the immune system. Immunization with the self-peptides displayed on the surface of a VLP has been proven to produce high-titer antibodies to the self-antigen [26–29]. In 2007, Peng et al. developed the first human IgE peptide-based VLP vaccine [15]. Three peptides were selected from human IgE receptor-binding sites located in Cε3 domain. The conjugate vaccine was obtained by coupling the three synthetic peptides to the carrier protein hepatitis B surface antigen. Sera from vaccine-immunized rats contained high titers of antibodies, which reacted with human IgE. As the peptides are derived from IgE receptor-binding sites, the antibodies induced by the vaccine did not react with receptor-bound IgE, suggesting that the antibodies do not cause histamine release from basophils or mast cells. Moreover, the sera also cross-reacted with mouse, rat, and dog IgE with low titers. Furthermore, the sera inhibited the binding of human IgE or mouse IgE to its receptor in a dose-dependent manner [15]. These results were very encouraging and paved the way for further studies in the field.

In order to develop the ideal target of vaccine therapy, several IgE peptide antigens were rationally designed, using structural information for IgE and its interaction with the high-affinity receptor such that the anti-IgE antibodies induced by the vaccine will bind free IgE, but not interact with IgE bound to cell surface receptors, thus avoid triggering the release of inflammatory mediators through IgE receptor cross-linking [16].

Through extensive screening in mice, two peptides were selected for further development. Screening involved immunization of mice with peptides conjugated to VLP that is derived from Q-beta bacteriophage (Qb-VLP), *ex vivo* assessment of antisera by enzyme-linked immunosorbent assay (ELISA) for high titers of antibodies recognizing human IgE, and, finally, *in vivo* functional assessment of rate of clearance of human IgE after bolus administration to mice. These two peptides were also evaluated to ensure that induced antibodies do not cause degranulation of FcεRI receptor-expressing cells through binding to receptor bound IgE and that they do not induce a T-cell activation. The selected peptides, named peptide Y and peptide P, were derived from different components of the Cε3 domain of IgE. Peptide Y represents the epitope recognized by omalizumab while peptide P corresponds to a different loop on IgE Cε3 domain [16]. Administration of the two conjugates mixed in equal proportions and adjuvanted with alum in mice produced high levels of IgE-specific antibody that bound to free but not receptor-bound human IgE and enhanced the rate of clearance of human IgE after a bolus injection into immunized mice [16].

Recently, the anti-IgE Qb-VLP conjugate vaccine was evaluated for *in vitro* stimulation of human peripheral blood mononuclear cells (PBMCs) and *in vivo* immunogenicity in mice. Qb-VLPs are obtained by the self-assembly of multiple Qb capsid protein monomers, a process which traps a large amount of bacterial ribonucleic acid (RNA) in the core of the VLP [30]. Bacterial RNA is known to activate the innate immune system via Toll-like receptor-7 (TLR7) and Toll-like

receptor-8 (TLR8) found within the endosomes of certain immune cells and has been shown to contribute to the immunogenicity of Qb-VLP vaccines. The *in vitro* secretion of interferon-α (IFN-α) from human PBMCs exposed to the vaccine is consistent with TLR7 activation. Moreover, immunization of mice with the IgE peptide Qb-VLP conjugates induced high titers of anti-IgE antibodies in wild-type mice, but significantly lower titers in TLR7 knockout mice, supporting the self-advanting role of the RNA. Addition of alum and alum/cytosine-phosphate-guanosine (CpG) as adjuvants partially or completely compensated for the lack of TLR7 activation in TLR7-deficient mice. This study demonstrated the key role that TLR7 plays in the immunogenicity of the IgE peptide Qb-VLP conjugate vaccine [30].

In rodent species, the human vaccine cannot be used to assess function directly due to lack of homology; however, species-specific mimetic vaccines containing murine homologues of the Y and P peptides conjugated to Qb-VLP were shown to be capable of inducing anti-IgE antibodies than can lower serum IgE in a murine allergy model [16]. Similarly, peptides derived from Cε3 domain of canine IgE were shown to induce anti-IgE and have therapeutic effect in dog allergy models [31,32].

Recently, as part of preclinical evaluation of the vaccine to optimize formulation and dose prior to initiating clinical studies, anti-IgE vaccine was evaluated in non-human primates (NHP) [17]. Cynomolgus monkey (*Macaca fascicularis*) was chosen as the NHP model considering that there is an 85% sequence homology between human and cynomolgus IgE constant region with a 100% homology for the P peptide and only single amino acid difference for the Y peptide [33]. Weeratna et al. evaluated tolerability and immunogenicity of the two Qb-VLP peptides Y and P, the effect of adjuvants (alum and/or CpG), and the efficacy in reducing circulating IgE in NHP. All vaccine formulations appeared to be well tolerated [17]; these results are consistent with observations derived from trials that used the same adjuvant and carrier components in NHP and humans at similar or higher doses [34–36]. The vaccine-induced anti-IgE antibodies resulted in significant lowering of serum IgE levels in many of NHPs, with some animals achieving as much as 80% lower IgE compared to baseline [17].

Despite these promising results, the degree of IgE lowering in NHP was less than that seen with omalizumab in humans [17]; however, the differences in species and potential mechanism of action make it hard to predict how this would translate into humans. Therefore, a decision was made to advance this anti-IgE vaccine into human clinical testing.

2.2. Early clinical development

In 2012, the first-in-human interventional phase 1, randomized, double-blinded, placebo-controlled study (NCT01723254) was performed to assess the safety and tolerability of different doses of an anti-IgE vaccine in 189 adult subjects with allergic rhinitis (AR) [37]. Two intramuscular formulations at different ascending doses (6, 20, 60, or 200 mcg total) combined with fixed adjuvants doses of either alum

(0.5 mg) [PF 06444753 (IGE-1)] or alum plus TLR9 agonist CpG 24555 (0.5 mg each) [PF 06444752 (IGE-2)] were investigated [37]. With the exception of transient injection site local reactions, only two serious adverse events were reported and eight cases of treatment-emergent adverse events were closely related to active treatment [37]. Presented at the 2016 Annual Meeting of the American Academy of Allergy, Asthma and Immunology, the results of this trial indicated that both anti-IgE vaccines were generally well-tolerated and induced anti-IgE specific antibodies; however, no significant benefit with CpG included in terms of immunogenicity and modest lowering of serum IgE levels was seen in the majority of subjects [18]. Thus, the development of the vaccine has been actually discontinued.

3. Conclusion

IgE has become a major therapeutic target for allergic diseases. Despite the availability of multiple treatment modalities, including the most recent anti-IgE biological therapies, current research is aimed to discover new strategy by vaccines. Although at early stage of research, the development of an anti-IgE vaccine could provide clinical benefits by triggering human immune system to produce therapeutic anti-IgE antibodies, potentially representing a further step forward in the treatment of allergic diseases.

4. Expert opinion

Given the multifaceted effector functions of IgE in immediate hypersensitivity, late-phase reactions, regulation of IgE receptor expression, and immune modulation, IgE antibodies have long represented an attractive target for therapeutic agents in asthma and other allergic diseases. Omalizumab, the flagship of anti-IgE mAb, is the first biological therapy approved for uncontrolled allergic asthma in children and adults and for CSU in adolescents (aged ≥ 12 years) and adults who remain symptomatic despite H_1 antihistamine treatment [38,39]. Recent clinical observations have also expanded its evidence of efficacy and safety in several *off-label* allergic and non-allergic disease (i.e. AR, atopic dermatitis, food allergy, non-atopic asthma, etc.) [40–42]. Experimental evidence derived from omalizumab studies has also shed new light on the role of IgE in the cellular and molecular mechanisms underlying airway remodeling and in innate immune (antiviral) homeostasis [8]. Although the effectiveness and safety profile of omalizumab have been consolidated in asthma therapy, there are several issues needing additional investigations, such as the optimal duration of treatment with omalizumab, the adherence to prolonged treatment, the eventual sustained efficacy after the end of treatment, the comprehensive impact of omalizumab therapy on the natural history of asthma especially in children, the identification of biomarker of response, and the cost issue.

The need to overcome some of these limitations of omalizumab has recently prompted the development of a generation of new anti-IgE antibodies. QGE031 (ligelizumab) is a novel humanized IgG1 mAb against human IgE, which binds to the

C ϵ 3 domain of IgE with 50-fold higher *in vitro* and 6- to 9-fold greater *in vivo* affinity than omalizumab. After positive results of two phase I clinical trials investigating its pharmacological properties and safety, a phase II randomized, double-blind, placebo-controlled parallel-group multicenter trial comparing the effects of QGE031 with those of omalizumab in adult patients with mild allergic asthma have also demonstrated an enhanced suppression of allergen-induced responses in the airways [43,44]. Therapeutic areas of QGE031 have been expanded to other allergic and non-allergic disease such as CSU, atopic dermatitis, peanut allergy, and active bullous pemphigoid with limited available results. Another high-affinity anti-IgE antibody (MEDI4212) was generated with the potential to both neutralize soluble IgE and eliminate IgE-expressing B-cells through antibody-dependent cell-mediated cytotoxicity. In addition to neutralizing free IgE, the effect of long-term reduction of IgE synthesis confers to MEDI4212 the potential to exceed the current limits of omalizumab and to widen the treatable population of severe asthmatics, even with very high IgE levels [45]. However, the results of the phase I study of MEDI4212 in atopic subjects highlighted a limited potential for dosing schedule advantage over omalizumab [46]. Finally, the approach of upstream targeting the IgE pathway has led to the conception of an anti-C ϵ mX domain antibody, which targets IgE-expressing B lymphocytes by binding to membrane-bound IgE (mIgE) on IgE-switched cells, lysing mIgE-expressing B lymphoblasts, thus preventing the allergen-induced generation of IgE-producing plasma cells [47]. The safety, tolerability, and activity of anti-C ϵ mX have been demonstrated in phase I and II clinical trials of quilizumab [48,49]. Quilizumab is a humanized, monoclonal IgG1 that binds to the M1-prime segment present only on membrane IgE, but not on soluble IgE in serum [50]. The efficacy, safety, and pharmacokinetics of quilizumab were recently evaluated in adults with uncontrolled allergic asthma. At the end of treatment, quilizumab was well tolerated with a safety profile consistent with previous clinical studies; however, quilizumab treatment did not result in a clinically significant impact on exacerbation rate, lung function, or quality of life [51].

Outside the area of development of new humanized anti-IgE mAbs, the research field of therapeutic IgE-targeted vaccines holds potential benefits for the treatment of allergic diseases. The use of a therapeutic anti-IgE vaccine may offer long-term efficacy reducing costs, increasing patients' compliance and safety, and potentially modifying the course of the allergic diseases in comparison with current available biological therapy. Moreover, this strategy might be also useful to serve as a potential preventive protection for children who are at a high risk of developing allergic diseases. However, most of the experimental observations in animal models have not yet been translated into new treatments. At the same time, some potential concerns on the strategy using anti-IgE vaccines could be raised: the potential increased risk of helminth infections, of type III hypersensitivity reactions due to the formation of immune complexes, and, mostly, the impossibility to instantly stop anti-IgE antibodies production if they are no longer required. At the moment, all these issues of efficacy and safety require to be further investigated.

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References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

- Ishizaka K, Ishizaka T Identification of IgE. *J Allergy Clin Immunol*. 2016;137:1646–1650.
- The article recalls the story of the discovery of IgE by Ishizakas in USA.**
- Johansson SG The discovery of IgE. *J Allergy Clin Immunol*. 2016;137:1671–1673.
- The article recalls the story of the simultaneous discovery of IgE by Johansson in Sweden, who described an atypical myeloma protein that turned out to be physicochemically identical to the Ab the Ishizakas discovered.**
- Oettgen HC Fifty years later: emerging functions of IgE antibodies in host defense, immune regulation, and allergic diseases. *J Allergy Clin Immunol*. 2016;137:1631–1645.
- This review discusses the established mechanisms of action of IgE in pathologic immediate hypersensitivity, as well as its multifaceted roles in protective immunity, control of mast cell homeostasis, and its more recently revealed immunomodulatory functions.**
- Platts-Mills TA, Schuyler AJ, Erwin EA, et al. IgE in the diagnosis and treatment of allergic disease. *J Allergy Clin Immunol*. 2016;137:1662–1670.
- Ciprandi G, Marseglia GL, Castagnoli R, et al. From IgE to clinical trials of allergic rhinitis. *Expert Rev Clin Immunol*. 2015;11:1321–1333.
- Licari A, Marseglia G, Castagnoli R, et al. The discovery and development of omalizumab for the treatment of asthma. *Expert Opin Drug Discov*. 2015;10:1033–1042.
- Licari A, Marseglia A, Caimmi S, et al. Omalizumab in children. *Paediatr Drugs*. 2014;16:491–502.
- Samitas K, Delimpoura V, Zervas E, et al. Anti-IgE treatment, airway inflammation and remodelling in severe allergic asthma: current knowledge and future perspectives. *Eur Respir Rev*. 2015;24:594–601.
- This review highlights recent findings supporting the notion that anti-IgE treatment modulates the complex immune responses that manifest clinically as asthma and ameliorates airway remodeling changes often observed in allergic severe asthma phenotypes.**
- Sattler C, Garcia G, Humbert M. Novel targets of omalizumab in asthma. *Curr Opin Pulm Med*. 2017;23:56–61.
- Marshall JS, Bell EB. Induction of an auto-anti-IgE response in rats I. Effects on serum IgE concentrations. *Eur J Immunol*. 1985;15:272–277.
- Marshall JS, Bell EB. Induction of an auto-anti-IgE response in rats III. Inhibition of a specific IgE response. *Immunology*. 1989;66:428–433.
- Marshall JS, Prout SJ, Jaffery G, et al. Induction of an auto-anti-IgE response in rats II. Effects on mast cell populations. *Eur J Immunol*. 1987;17:445–451.
- Hellman L. Profound reduction in allergen sensitivity following treatment with a novel allergy vaccine. *Eur J Immunol*. 1994;24:415–420.
- Stanworth DR, Jones VM, Lewin IV, et al. Allergy treatment with a peptide vaccine. *Lancet*. 1990;336:1279–1281.
- Peng Z, Liu Q, Wang Q, et al. Novel IgE peptide-based vaccine prevents the increase of IgE and down-regulates elevated IgE in rodents. *Clin Exp Allergy*. 2007;37:1040–1048.
- Champion BR, Stead DR, Wright P. IGE CH3 Peptide Vaccine. *US8722053* (2011)
- Weeratna RD, Chikh G, Zhang L, et al. Immunogenicity of a peptide-based anti-IgE conjugate vaccine in non-human primates. *Immun Inflamm Dis*. 2016;4:135–147.
- This article evaluates tolerability, immunogenicity and efficacy of the two Qb-VLP peptides Y and P in non-human primates.**
- Wong GY, Elfassi E, Girard G, et al. A phase 1 first-in-human study (b4901001) evaluating a novel anti-IgE vaccine in adult subjects with allergic rhinitis. *AAAAI-2016* 2016; abstr. 539. [cited 28th December 2016]. Available from: URL: [http://www.jacionline.org/article/S0091-6749\(15\)02412-4/fulltext](http://www.jacionline.org/article/S0091-6749(15)02412-4/fulltext)
- Vernersson M, Ledin A, Johansson J, et al. Generation of therapeutic antibody responses against IgE through vaccination. *Faseb J*. 2002;16:875–877.
- Li W, Joshi MD, Singhania S, et al. Peptide vaccine: progress and challenges. *Vaccines (Basel)*. 2014;2:515–536.
- Peng Z Vaccines targeting IgE in the treatment of asthma and allergy. *Hum Vaccin*. 2009;5:302–309.
- This review describes the state of the art of anti-IgE vaccines, recalling the pivotal studies for developing an effective vaccine targeting IgE.**
- Purcell AW, McCluskey J, Rossjohn J. More than one reason to rethink the use of peptides in vaccine design. *Nat Rev Drug Discov*. 2007;6:404–414.
- Wang CY, Walfield AM, Fang X, et al. Synthetic IgE peptide vaccine for immunotherapy of allergy. *Vaccine*. 2003;21:1580–1590.
- Ledin A, Bergvall K, Hillbertz NS, et al. Generation of therapeutic antibody responses against IgE in dogs, an animal species with exceptionally high plasma IgE levels. *Vaccine*. 2006;24:66–74.
- Jennings GT, Bachmann MF. The coming of age of virus-like particle vaccines. *Biol Chem*. 2008;389:521–536.
- Ma Y, Hayglass KT, Becker AB, et al. Novel recombinant interleukin-13 peptide-based vaccine reduces airway allergic inflammatory responses in mice. *Am J Respir Crit Care Med*. 2007;176:439–445.
- Ma Y, HayGlass KT, Becker AB, et al. Novel cytokine peptide-based vaccines: an interleukin-4 vaccine suppresses airway allergic responses in mice. *Allergy*. 2007;62:675–682.
- Jegerlehner A, Tissot A, Lechner F, et al. A molecular assembly system that renders antigens of choice highly repetitive for induction of protective B cell responses. *Vaccine*. 2002;20:3104–3112.
- Chackerian B, Lowy DR, Schiller JT. Conjugation of a self-antigen to papillomavirus-like particles allows for efficient induction of protective autoantibodies. *J Clin Invest*. 2001;108:415–423.
- Akache B, Weeratna RD, Deora A, et al. Anti-IgE Qb-VLP conjugate vaccine self-adjuvants through activation of TLR7. *Vaccines (Basel)*. 2016;4:pii: E3.
- Morsey MA, Sheppard MG, Wheeler DW. Anti-IgE Vaccines. *US8273356* (2012)
- T. T IgE peptide vaccine. *US20150203550* (2015)
- Clark D, Shiota F, Forte C, et al. Biomarkers for non-human primate type-I hypersensitivity: antigen-specific immunoglobulin E assays. *J Immunol Methods*. 2013;392:29–37.
- Maurer P, Bachmann FM. Immunization against angiotensins for the treatment of hypertension. *Clin Immunol*. 2010;134:89–95.
- Cornuz J, Zwahlen S, Jungi WF, et al. A vaccine against nicotine for smoking cessation: a randomized controlled trial. *PLoS One*. 2008;3:e2547.
- Cooper CL, Davis HL, Morris ML, et al. Safety and immunogenicity of CpG 7909 injection as an adjuvant to Fluorix influenza vaccine. *Vaccine*. 2004;22:3136–3143.

37. A Study To Assess The Safety And Tolerability Of Different Doses Of PF-06444753 And PF-06444752 In Subjects With Allergic Rhinitis. [cited 28th December 2016]. Available from: <https://clinicaltrials.gov/ct2/show/study/NCT01723254?term=NCT01723254&rank=1§=Xab3756>
38. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43:343–373.
39. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy*. 2014;69:868–887.
40. Marseglia GL, Merli P, Caimmi D, et al. Nasal disease and asthma. *Int J Immunopathol Pharmacol*. 2011;24:7–12.
41. Licari A, Castagnoli R, Bottino C, et al. Emerging drugs for the treatment of perennial allergic rhinitis. *Expert Opin Emerg Drugs*. 2016;21:57–67.
42. Garcia G, Magnan A, Chiron R, et al. A proof-of-concept, randomized, controlled trial of omalizumab in patients with severe, difficult-to-control, nonatopic asthma. *Chest*. 2013;144:411–419.
43. Arm JP, Bottoli I, Skerjanec A, et al. Pharmacokinetics, pharmacodynamics and safety of QGE031 (ligelizumab), a novel high-affinity anti-IgE antibody, in atopic subjects. *Clin Exp Allerg*. 2014;44:1371–1385.
44. Gauvreau GM, Arm JP, Boulet LP, et al. Efficacy and safety of multiple doses of QGE031 (ligelizumab) versus omalizumab and placebo in inhibiting allergen-induced early asthmatic responses. *J Allergy Clin Immunol*. 2016;138:1051–1059.
45. Nyborg AC, Zacco A, Ettinger R, et al. Development of an antibody that neutralizes soluble IgE and eliminates IgE expressing B cells. *Cell Mol Immunol*. 2016;13:391–400.
46. Sheldon E, Schwickart M, Li J, et al. Pharmacokinetics, pharmacodynamics, and safety of MEDI4212, an anti-IgE monoclonal antibody, in subjects with atopy: a phase I study. *Adv Ther*. 2016;33:225–251.
47. Liour SS, Tom A, Chan YH, et al. Treating IgE-mediated diseases via targeting IgE-expressing B cells using an anti-CemX antibody. *Pediatr Allergy Immunol*. 2016;27:446–451.
48. Gauvreau GM, Harris JM, Boulet LP, et al. Targeting membrane-expressed IgE B cell receptor with an antibody to the M1 prime epitope reduces IgE production. *Sci Transl Med*. 2014;6:243ra85.
49. Harris JM, Maciucă R, Bradley S, et al. Efficacy and safety of quilizumab in adults with allergic asthma inadequately controlled on inhaled corticosteroids and a second controller (COSTA Study). *Am J Respir Crit Care Med*. 2015;191:A5168.
50. Brightbill HD, Lin YL, Lin Z, et al. Quilizumab is an afucosylated humanized anti-M1 prime therapeutic antibody. *Clin Anti-Inflamm Anti-Allergy Drugs*. 2014;1:24–31.
51. Harris JM, Maciucă R, Bradley MS, et al. A randomized trial of the efficacy and safety of quilizumab in adults with inadequately controlled allergic asthma. *Respir Res*. 2016;17:29.