

Recent Advances in the Development of Anti-allergic Drugs

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ABSTRACT

Research over the past decade has provided information concerning the onset and treatment of allergic diseases, including bronchial asthma, allergic rhinitis and atopic dermatitis. Recent studies also indicated that allergic inflammation is the basic pathophysiology of allergic diseases and is closely associated with their progression and exacerbation. Our understanding of the mechanism of allergic inflammation with regard to therapeutic agents has improved as a result of immunological and molecular biological studies. While much effort has been paid to developing a new anti-allergic drug, allergic disease has yet to be completely conquered. More extensive research will allow the development of new therapeutics to combat allergic diseases. This article provides an overview of recent advances in the development of anti-allergic drugs.

KEY WORDS

anti-allergic drug, antihistamine, leukotriene inhibitor, Th2 cytokine inhibitor, thromboxane A₂ inhibitor

INTRODUCTION

The increasing incidence in allergic diseases, including allergic bronchial asthma, allergic rhinoconjunctivitis and atopic dermatitis, is as yet unexplained. Pathomechanistic studies have indicated that allergic inflammation contributes to onset of acute and/or chronic symptoms of allergic diseases. Despite our understanding of the underlying mechanism, there are some therapeutic problems because the prevalence of allergic diseases has increased dramatically in recent decades.¹⁻⁵ A significant amount of research is currently focused on explaining this rise in the number of cases of allergic diseases.⁶⁻¹⁵

Bronchial asthma, a typical allergic disease, is thought to be caused by subchronic eosinophilic epithelial desquamative inflammation of the airway. Other allergic diseases such as allergic rhinitis and atopic dermatitis are also inflammatory diseases, as indicated by the names. Thus, allergic inflammation is the basic pathophysiology of allergic diseases and is closely associated with progress and exacerbation of the diseases.

Based on the information described above, a suitable target for the therapeutic treatment of allergic diseases might be the suppression of allergic inflam-

mation. As shown in Figure 1, allergic inflammation is initiated by the activation of adoptive immune response. This immune system results from allergen impact on the mucosal surface. Whole allergen is taken up by antigen-presenting cells and peptides are presented to T cells, resulting in T cell activation and elaboration of cytokines. This is the onset of immune response to produce immunoglobulin. In a Type I allergic reaction, immunoglobulin E (IgE) is produced, which is fixed to the mast cell through Fcε receptor. Cross-linking of allergen-specific IgE leads to the release of histamine, leukotrienes (LTs) and prostaglandin D₂ from mast cells. These chemical mediators introduce immediate phase reactions such as bronchospasm, sneezing and itching in the tissues. Interleukin-4 (IL-4), IL-13 and other mediators including chemokines are generated and released almost 3 to 12 hours after the antigen-antibody combination. Chemokines attract the eosinophils to the allergic lesion. Eosinophil recruitment leads to the release of toxic proteins and mediators, such as protease and LTs, causing edema and epithelial cell damage. Then, tissue remodeling, the repair of injured tissue, occurs. From these basic concepts, current therapeutic approaches have focused either on the treatment of allergic inflammation or the rapid relief of severe

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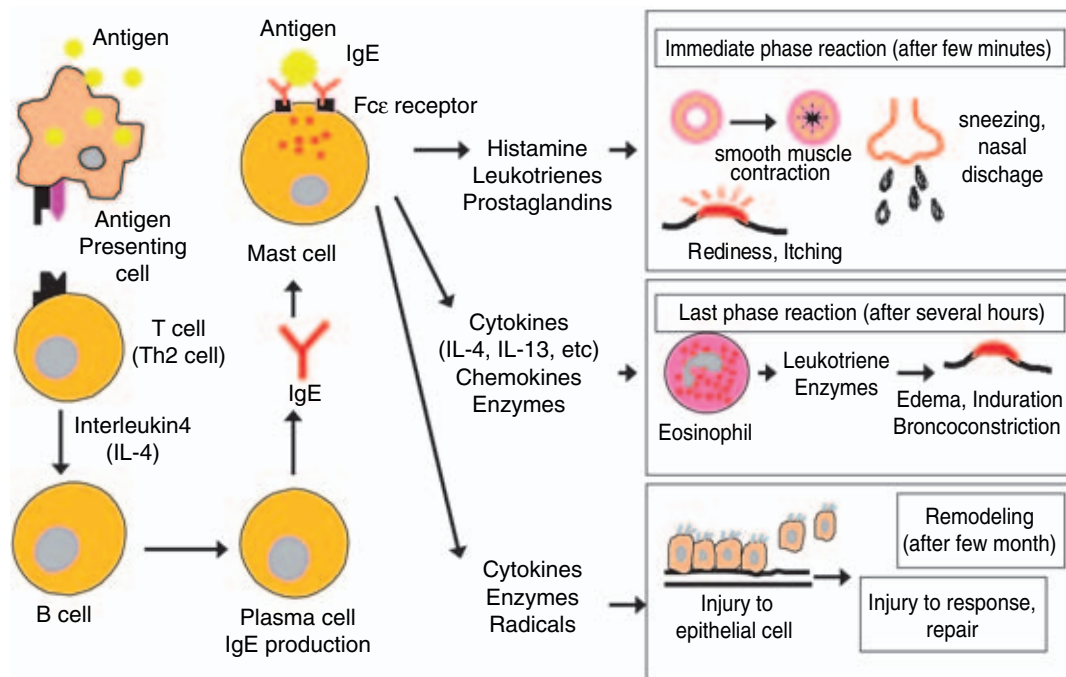


Fig. 1 The mechanism of IgE mediated allergic reaction

Table 1 The classification of anti-allergic drugs (anti-asthma drug)

Classification	Medication	Drugs
Controllers	1. Taken daily on a long-term basis 2. Prophylactic and preventive medication	1. Inhaled glucocorticoids 2. Anti-allergic agents [Anti-histamine, Leukotriene inhibitor, Thromboxane A ₂ inhibitor, Th2 cytokine inhibitor, Mast cell stabilizer, etc.]
Relievers	1. Taken on demand 2. Quick relief for the severe symptoms	1. Rapid-acting inhaled β_2 -agonists 2. Systemic glucocorticoids 3. Anti-cholinergics 4. Methylxanthines

Table 2 Histamine receptor

Receptors	Expression	Agonist	Antagonist
H1	Nerve cells, airway and vascular smooth muscles, neutrophils, eosinophils, monocytes, DC, T and B cells, etc.	2-methyl histamine	Ethanolamine
H2	Nerve cells, airway and vascular smooth muscles. Neutrophils, eosinophils, monocytes, DC, T and B cells, etc.	4-methyl histamine	Cimetidine Ranitidine
H3	Histaminergic neurons, eosinophils, DC, monocytes Low expression in peripheral tissues	α -methyl histamine	Thioperamide Imupromidine
H4	Eosinophils, neutrophils, DC, T cells, Basophils, mast cells Low expression in nerve cells, hepatocytes, peripheral tissues	—	—

symptoms.¹⁶⁻²⁰ The former kind of therapeutics are called “controller” and the later type are called “reliever.” The typical controller is topical glucocorticoid

and the reliever is a bronchodilator and anti-histamine. The classification and typical characters of both kinds of drug are outlined in Table 1.

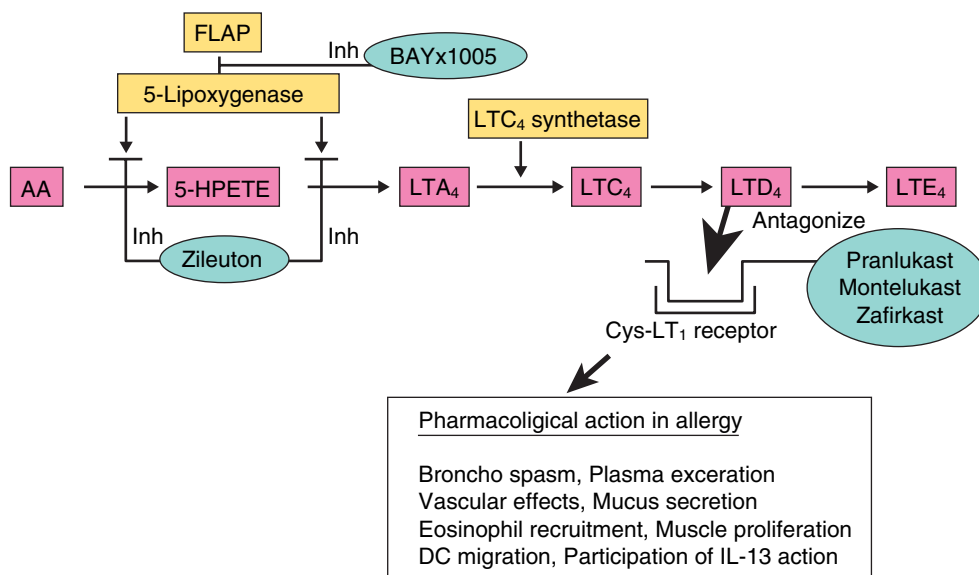


Fig. 2 The 5-lipoxygenase (5-LO) pathway of arachidonic acid (AA) and inhibitors. FLAP: 5-lipoxygenase activating protein, 5-HPETE: 5-Hydroperoxyeicosatetraenoic acid, DC: dendritic cell, Inh: Inhibition

Table 3 Summary of present status and recommendations for third generation antihistamines by CONGA

- 1) The anti-inflammatory or anti-allergic properties should be demonstrable *in vivo* in humans, at therapeutic doses and under natural exposure to the offending allergens
- 2) The therapeutic index of an antihistamine, defined as its benefit-risk ratio, is a more important concept than either potency (preclinical studies) or efficacy (clinical trials)
- 3) The lack of cardiac toxicity must be retained in the development of novel congeners that enter the market in the future
- 4) The drug should not affect any CYP isozyme function, should not displace protein bound medications and should not affect active transport mechanism (*i.e.* P-glycoprotein)
- 5) Non-sedative properties should be defined by measuring a) incidence of subjective sleepiness b) objective cognitive and psychomotor function c) positron emission tomography (PET) measurement of H1 receptor occupancy
- 6) A new antihistamines based on the theoretical properties should however, be proven to have distinct clinical advantage over existing drugs

There are numerous discussions concerning a suitable nomenclature of anti-allergic drugs. The nomenclature can reflect the target cells and molecules which participate at the onset and development of allergic diseases. Therefore, in this manuscript, anti-allergic drugs involve antihistamines, leukotriene inhibitors, thromboxane inhibitors, Th2 cytokine inhibitors, mast cell stabilizers and agents for new tar-

get cells or molecules. The recent advances of therapeutic agents for allergic diseases will be described in this manuscript.

ANTI-HISTAMINES

During the past decade, there have been major advances in our understanding of histamine, histamine receptors and histamine H1 antagonists. Histamine has played a central role in our understanding of allergic reaction. It was the first mediator to be associated with allergic reaction and was the first whose inhibition proved useful in the management of diseases. For many years, histamine receptors have been characterized using a pharmacological approach. Recently, a cDNA clone encoding the H1 receptor has been cloned in human leukocytes and the structure of the H1 receptor protein has been deduced along with several other histamine receptors (Table 2). These findings improved the development of new antihistamines, especially H1 receptor antagonists.

The first-generation antihistamines were defined by their H1 receptor blocking activity, and despite pronounced unwanted side-effects they are still widely used.²¹⁻²⁵ The problems with systemic side-effects, especially sedation and dry mouth, stimulated the pharmacological research to develop a second generation of drugs that were ostensibly free of these properties and more efficacious.

The second-generation antihistamines are called non-sedating H1 antagonists because of their low penetration through the blood-brain barrier. Compared with the first generation agents, they are

Table 4 The inhibitors of leukotrienes

	5-LO inhibitor	Cys LT1 antagonist		
	Zeileuton	Zafielkast	Monterukast	Pranlukast
Oral Dosage (mg/day)	600	40	10	450
Administration (times/day)	4	2	1	2
Synergistic effect to steroid	+	+	++	++
Suppression of eosinophilia	+	+	++	++
Asthma	++	++	++	++
Allergic Rhinitis	ND	ND	ND	++
Metabolism	—	CYP2C9	CYP3A4 CYP2C9	CYP3A4

5-LO: 5-lipoxygenase Cys LT1: cystenyl leukotriene 1 receptor ND: Not done

Table 5 The role of thromboxane A2 in allergic condition in human and experimental animals

1. Allergic bronchial asthma—late asthmatic response
2. Allergic rhinitis—sneezing, rhinorrhea, rhinostenosis
3. Atopic dermatitis — the relationship between TP polymorphism and IgE production
4. Allergic conjunctivitis

known for their minimal central nervous system effect. Many of the second-generation antihistamines undergo extensive first pass metabolism in the liver by the cytochrome p450 (CYP) enzymes. Drugs such as ketoconazole, erythromycin and azithromycin, which affect the activity of CYP, can lead to build up of the parent antihistamine compound, thus increasing the risk of side-effects. It has been demonstrated that the ingestion of grapefruit juice can inhibit isoenzyme CYP3A in the liver. Thus grapefruit juice may increase the concentration of antihistamines, such as terfenadine, loratadine and astemizole which are metabolized by CYP3A4.

Additionally, life-threatening adverse cardiac side effects, QT prolongation and torsades de pointes ventricular tachyarrhythmia have been demonstrated to be associated with the use of some second-generation antihistamines. These effects are due to the direct blockade of a specific class of potassium channels controlling the repolarization phase of the cardiac action potential and are not related to the blockade of H1 receptor. Thus this cardiotoxicity by second-generation antihistamines is not a class effect.

As a direct result of these problems, a third-generation anti-histamines has emerged.²⁶ The term 'third-generation' or 'multifunctional' antihistamine was employed by Hanifin,²⁷ Sabbah,²⁸ Caproni *et al.*²⁹ and ourselves³⁰ for describing the pharmacological profiles of ketotifen, terfenadine and cetirizine, respectively. However, clear criteria of what this term means are still uncertain. In 2003, a Consensus Group on New Generation Antihistamines (CONGA) has been set up with the support of the 'British Soci-

Table 6 Clinical and basic pharmacological profile of Sup-latast

1. Decrease in the number of eosinophils in sputum of asthmatic patients and in blood of atopic dermatitis patients
2. Decrease in serum IgE level in allergic asthma, allergic rhinitis and atopic dermatitis patients
3. Decrease in the production of Th2 cytokines by T cells from allergic patients
4. Inhibition of IgE production in mice and rats
5. Inhibition of the production of Th2 cytokines by murine splenocytes
6. Inhibition of the onset and development of experimental allergic asthma, rhinitis, dermatitis and eosinophilia in mice, rats and guinea pigs

ety for Allergy and Clinical Immunology' to address the meaning of the third-generation antihistamines. An internal expert panel of scientists and clinicians outside the pharmaceutical industry convened to form a CONGA and reported in *Clin. Exp. Allergy*, 2003.²⁶ An exclusive summary was produced with recommendations in six areas as indicated in Table 3.

Published information concerning H1 antihistamines suggests that none of them can be classified as a true third-generation antihistamine. Rationalization is required to develop a new class of antihistamines.

LEUKOTRIENE INHIBITORS

LTs are derived from membrane constituent arachidonic acid and induce many allergic symptoms, including airway smooth muscle contraction, hypersecretion, eosinophilia and airway wall remodeling.³¹⁻³⁵

As shown in Figure 2, recent research revealed the additional biological activity of LTs in allergic reaction. One explanation is the role of LTs in dendritic cell (DC) migration³⁶ and another is the participation of LTs in the pathological action of IL-13.³⁷ Recent studies by Robbani *et al.*³⁶ indicated that LTs play a role in the antigen-stimulated migration of DC through the activation of multidrug resistance-associated protein 1 (MRP 1) and chemokine

Table 7 New cellular and molecular targets and concomitant approaches for anti-allergic drug development

Target	Approach
Allergen	Epitopes, TCR activation status receptors
Protease	Tryptase, Elastase, Kimase, MMP inhibitors
T cell modulator	(Th2) GATA-3, FOG-1, CD28, CTLA-4 (Th1) CpG oligodeoxynucleotides, T-bet (T) Macrocyclic immunosuppressant
Cytokines	TNF antagonist, GM-CSF antagonist, IL-4 antagonist, IL-5 antagonist, IL-13 antagonist, IL-10, IL-12, IL-18, IFN- γ
Chemokines	Th2 related chemokines receptor antagonist, CCR-3 antagonist, IL-8 receptor antagonist
Adhesion molecule	VLA-4 antagonist, selectin antagonist, ICAM-1 and VCAM-1 antagonists
IgE antibody	Humanized anti-IgE antibodies
Small molecules	Cys LT1 and LT2 antagonist, 5-LO inhibitor, LTB ₄ antagonist, H ₁ receptor antagonists, Kinin receptor antagonist, endothelin antagonist, Tachykinin antagonist, Anti-oxydant, P2Y receptor antagonist

(CCL19). This suggests that LT may play a role in the acceleration of antigen presentation in acquired immunity. In addition, IL-13 induced airway remodeling in mice through the generation of LTs which is the main cause of the onset of airway hyperreactivity, eosinophilia and MUC5AC production. This suggests that IL-13 plays an important role in the onset of airway hyperreactivity and contributes to the stimulation of LT generation.

Evidence from several sources indicates an additional role for LTs in allergic diseases. After the identification of the chemical structures of LTs, extensive efforts have been made for cloning of the cysteinyl LT (cys-LT) receptors. It is noteworthy that the launch of LT antagonists preceded the identification and cloning of cys-LT receptors. On this basis, many researchers initiated programs to find either inhibitors of LT biosynthesis or selective receptor antagonists.

In the 1990s, the LT approach moved from concept to proof. This was based on the successful development and subsequent launch of three LT antagonists and one 5-lipoxygenase (5-LO) inhibitor listed in Table 4. Three receptor antagonists display significant structured homology and are highly effective against LTD₄. A common feature of clinical trials with these three antagonists is an improvement in baseline lung function in asthma patients but not in non-asthma patients. This result demonstrates that antagonists do not have a direct relaxing activity of bronchial smooth muscle. These improvements are generally in the range of 25–50%, although the magnitude of the changes depends on the symptoms which are measured by the severity of disease. In addition, many studies have been carried out with combinations of cys-LT antagonists and inhaled corticosteroid.³⁸⁻⁴⁰ Generally, treatment of LT antagonists resulted in a lower dose of inhaled corticosteroid, reducing the severity of asthmatic symptoms.

As for 5-LO inhibitors, many compounds have been developed but only one drug, zileuton has been regis-

tered for treatment of asthma in the USA. From observations with 5-LO inhibitors, in particular zileuton, it appears that the anti-asthmatic effects of 5-LO inhibition and selective cysLT1 receptor antagonists in asthma patients are indistinguishable. The successful induction of cys-LT1 receptor antagonists and 5-LO inhibitors for the treatment of bronchial asthma provided clinical data that confirmed the LT hypothesis in asthma, which had taken almost 70 years to evolve since the original discovery of slow reacting substance of anaphylaxis.

Unfortunately the clinical role of LTs in other allergic diseases, such as allergic rhinitis and dermatitis, is still uncertain. Our studies employing 5-LO gene deficient mice⁴¹ suggest low participation of LTs in allergic dermatitis and IgE production (unpublished data). Further studies to investigate the role of LTs in other allergic diseases, especially nasal obstruction, could expand the therapeutic utility of LT inhibitors.

THROMBOXANE A₂ (TXA₂) INHIBITORS

There is some evidence from basic research and clinical reports to indicate that TxA₂ is involved in the onset and development of allergic diseases as shown in Table 5.⁴²⁻⁴⁵ There are two types of TxA₂ inhibitor in clinical use in Japan, including one TxA₂ synthetase inhibitor (ozagrel) and two TxA₂ receptor antagonists (ramatroban and seratrodust). All these TxA₂ inhibitors are employed for the treatment of bronchial asthma. The efficacy of these agents in asthma treatment is still under discussion, but the effectiveness of ramatroban in allergic rhinitis is noteworthy. Because of the strong expression of TxA₂ receptor mRNA in the nasal mucosa of allergic rhinitis patients and the positive relationship between TxA₂ receptor polymorphism and IgE production,⁴⁶ the anti-allergic action of TxA₂ receptor antagonist might be anticipated. From the extensive basic and clinical investigations concerning the efficacy of ramatroban in allergic rhinitis, the drug showed a potent therapeutic ac-

tivity to several nasal symptoms, especially, nasal obstruction. Since several investigators including ourselves, revealed the efficacy and antagonistic action of ramatroban against CRTH 2, one of the prostaglandin D2 receptors, interest in the role of CRTH2 in the onset of nasal obstruction has increased.^{42,44} However, further studies are necessary to fully determine the efficacy of these anti-CRTH2 agents.

TH2 CYTOKINE INHIBITOR

There is now good evidence that allergic diseases are driven by antigen specific Th2 cells. Recent advances in understanding the immunology of Th2 cells have opened up the possibility of specific immunomodulation to control allergic diseases. Our laboratory, in collaboration with a pharmaceutical company, has investigated suplatast, a Th2 cytokine inhibitor.⁴⁷⁻⁵⁰ Suplatast initiates the suppression of IgE antibody production and eosinophilia by interfering with Th2 cytokine production. In addition, suplatast inhibits the activation of chloride ion channels on eosinophils resulting in cell death (unpublished data). The clinical and basic pharmacological profile of suplatast is summarized in Table 6. This is the first trial to apply the T cell immunomodulator as a remedy for allergic diseases.

FUTURE DRUGS

Future strategy aimed at down regulation of the allergic response can be classified into many categories as indicated in Table 7. While there are numerous possible strategies to develop a new drug, our interest is focused on the concept of Th2 dependent allergic inflammation in the diseases.

With regard to the suppression of Th2 response, there are some new trials targeting Th1 response stimulation, cytokine suppression and other regulatory molecules. One of the Th1 stimulators is a plasmid vector containing genes that encode allergen, namely a DNA vaccine.^{51,52} This vaccine decreases Th2-mediated responses, enhances Th1 mediated responses and suppresses allergic responses in animal models. Other trials have employed a virus-like particle to induce interferon producing CD8+T cells and mucosal DNA vaccines to induce tolerance.⁵³ For example, the main peanut allergen gene expression vector when administered orally caused higher fecal IgA and serum IgG2a and lowered serum IgE titer and resulted in decreased anaphylactic symptoms.⁵⁴ Whether this approach is efficacious will be determined in further studies.

A particular approach for enhancement of Th1 mediated response has been the administration of synthetic oligodeoxynucleotides with immunostimulatory sequences. Strong stimulation was driven by sequences containing methylated CpG motifs that are more highly expressed in microbial rather than

vertebrate DNA, and so are recognized as foreign by the Toll-like receptor in innate immunity. These motifs indicate the function as Th1 promoting adjuvant capable of switching the usual Th2 response toward Th1 response.⁵⁵⁻⁵⁷ Preclinical results are promising, but the outcome of clinical trials for allergic diseases is pending.

Some experimental results, including those of our own, indicate the efficacy of interferons or IL-12 against allergic inflammation.^{58,59} Contrary to basic research, these cytokines are ineffective for treating allergic diseases.^{60,61} These cytokines, along with related targets, will have to be monitored in near future. In addition to TH1 related cytokines, Th2 cytokines including IL-5 are the target molecule for anti-allergic agents. As for IL-5 suppression, there are many experiments to support the effectiveness of anti-IL-5 monoclonal antibody at inhibiting allergic diseases.⁶²⁻⁶⁶ We have demonstrated the efficacy of anti-IL-5 monoclonal antibody for allergic airway wall remodeling, but not for allergic airway hyperreactivity in experimental animals.⁶⁶ Our data is confirmed by some extensive clinical studies. Holgate *et al.* reported ineffectiveness of IL-5 monoclonal antibody in airway hyperreactivity but found it to be effective in the therapy for allergic eosinophilia.⁶⁷ Moreover, recent studies by Kay *et al.*⁶² indicated the effectiveness of anti-IL-5 antibody on airway wall remodeling in asthma patients. These results stimulated a discussion about the role of IL-5 and eosinophils in the development of allergic asthma. Long term treatment of anti-IL-5 will be necessary to establish the role of IL-5 and eosinophils in bronchial asthma. Regarding the role of eosinophils, our recent studies employing the inhibitors of eosinophil chemotaxis indicate the efficacy of eosinophil inhibitors for anti-asthmatic treatment (unpublished data).

As for IL-13 and IL-9, many investigators reported that these are potent pathological substances for allergic diseases. Therefore, these two cytokines are target molecules for anti-allergic agents.⁶³⁻⁶⁶ In fact, mice lacking the gene for IL-13 and IL-9 showed low hyperresponsiveness and airway inflammation, respectively. However, there has been no report about the efficacy of the inhibitors against these cytokines in clinical trials.

In the recent past the use of humanized anti-IgE antibodies has become a new therapeutic strategy for allergic diseases.⁶⁸ Treatment with anti-IgE antibodies leads to a decrease in serum IgE and in the number of high-affinity IgE receptors on mast cells and basophiles. These decreases lead to a low excitability of the effector cells reducing the release of inflammatory mediators. Anti-IgE antibody is expected to be a promising strategy in near future.

CONCLUSION

Considerable resources have been focused on reduc-

ing the incidence of allergic response by modifying existing therapeutics and developing new anti-allergic drugs. This manuscript reviewed the current state of play with regard to the development of anti-allergic drugs. Extensive research on the mechanism of allergy and therapeutics to combat allergic disease will give us an opportunity to find new strategies for establishing effective treatments. Continued research on the molecular mechanism of allergic disease will inevitably generate new forms of therapy.

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