

New perspectives in asthma treatment

The recent advances in the knowledge of the basic mechanisms underlying asthmatic inflammation have significantly contributed to the delineation of new therapeutic perspectives for asthma. There are currently three main approaches to the development of novel antiasthma treatments:

- 1) improvement in existing classes of drugs
- 2) identification of new compounds able to interfere with the complex network of proinflammatory mediators, cytokines, chemokines, and adhesion molecules involved in the pathogenesis of asthma
- 3) utilization of new forms of immunotherapy aimed at blocking the unbalanced Th2 response which characterizes the pathophysiology of asthma.

Such a remarkable expansion in available therapeutic options will probably allow us, over the next decade, to treat asthma by more selectively targeting the pathogenetic events responsible for this widespread airway disease.

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During the past 10 years, a growing body of evidence based on histologic, cytologic and biochemical studies has led to significant progress in our understanding of the pathophysiology of asthma. According to the current pathogenetic view, asthma develops as a consequence of an inflammatory response orchestrated by Th2 cells, in which mast cells, basophils, and eosinophils play a central role as both inducers and effectors (1). Airway epithelial cells are also crucial to the pathogenesis of asthma in that they respond to various phlogistic stimuli by expressing many pro-inflammatory proteins including mediators, enzymes, adhesion molecules, cytokines, and growth factors, thus leading to maintenance of asthmatic inflammation and airway remodeling (characterized by subepithelial collagen deposition, smooth-muscle and microvascular proliferation, and extracellular matrix alterations).

These recent advances have led us to consider inhaled corticosteroids the first-line drugs for long-term management of asthma, and, on the other hand, have also opened the way to the development of novel therapeutic strategies, actively pursued by pharmacologic and immunopharmacologic research. Such experimental

efforts should allow us soon to achieve a more specific antiasthma treatment.

This paper will outline the main directions of ongoing research, whose aims are to improve the potential of the drug classes already in use and to develop new therapeutic approaches, including pharmacologic and immunologic tools.

Improvements in existing classes of antiasthma drugs

Development of new steroids

Compelling evidence suggests that corticosteroids exert their effects on gene expression by two main mechanisms (2):

- 1) direct interaction of activated dimeric glucocorticoid receptors (GR) with specific DNA consensus sequences (GREs), leading to transactivation or transrepression of target genes (genomic effect)
- 2) interference with several transcription factors (e.g., NF- κ B, AP-1, and STAT) by either protein–protein interactions (at both cytoplasmic and nuclear levels) or other modalities (steric hindrance;

competition for overlapping nucleotide consensus sequences).

These latter nongenomic effects are clinically relevant because they represent the main pathway by which glucocorticoids carry out their anti-inflammatory and immunosuppressive action. In fact, many genes coding for proinflammatory proteins do not contain negative GREs.

Since the unwanted side-effects of glucocorticoids are mostly dependent on transactivation, an important strategy aimed at improving the therapeutic index (i.e., the ratio between desired and undesired pharmacologic effects) of inhaled corticosteroids is based on the development of new compounds (dissociated glucocorticoids) capable of retaining the nongenomic effects, but lacking the transactivation function. In this approach, a prototype molecule (RU24858) has been recently developed which is devoid of transactivating properties, but maintains the capability of inhibiting AP-1 and other transcription factors (3). Although preliminary *in vivo* studies suggest that this compound exhibits the same anti-inflammatory and immunosuppressive activity of the classic glucocorticoid prednisolone, such a pharmacologic approach presents some potential limitations for asthma therapy. In fact, transactivation of some relevant target genes, such as those encoding the β_2 -adrenergic receptor, lipocortin-1, I κ B, and other inhibitory proteins, also contributes to the overall antiasthmatic action of corticosteroids.

While this strategy of dissociation is being developed, a current method consists of increasing the therapeutic index of glucocorticoids by interfering with pharmacokinetic parameters in order to maximize topical activity and minimize systemic bioavailability. With regard to this aspect, the recently developed molecules (budesonide, fluticasone propionate, and mometasone furoate) have allowed us to overcome the problems related to gastrointestinal absorption, owing to both their low oral availability and very efficient first-pass hepatic metabolism (2). However, these drugs can still be absorbed from the respiratory tract into the systemic circulation. Therefore, a further pharmacokinetic improvement can be achieved either by the use of pharmaceutical preparations (e.g., liposomes) more selectively targeted to airway cells, or by increasing the rate of metabolic degradation in the bloodstream.

Selective phosphodiesterase (PDE) inhibitors

Recently, the therapeutic potential of theophylline as an antiasthma drug has been revalued in view of its supposed anti-inflammatory and immunomodulatory effects, which would occur at lower plasma levels than those required for bronchodilation (4). However, since PDE₄ is the predominant isoenzyme expressed by virtually all cell types involved in the pathogenesis of

asthmatic inflammation, selective PDE₄ inhibitors should significantly improve the therapeutic potential of theophylline, whose inhibitory action on the various PDE families is relatively weak and non-isoform-specific. According to recent *in vivo* studies, PDE₄ inhibitors display an impressive anti-inflammatory activity which is mainly, though not exclusively, directed toward eosinophils (5). Furthermore, second-generation inhibitors of the PDE_{4D} isoform (SB207499, V11294A) appear to have a more favorable therapeutic index than first-generation compounds (rolipram) that often induce nausea, vomiting, and gastric acid secretion.

New bronchodilators

Inhaled β_2 -adrenoceptor agonists

Inhaled β_2 -adrenoceptor agonists exhibit an excellent spasmolytic efficacy as well as a remarkable protective effect against bronchoconstrictor stimuli, and also have the advantage of being currently available as both short- and long-acting compounds. Therefore, it is quite difficult to imagine that further significant improvements of the present molecules may soon be realized.

K⁺ channel openers

K⁺ channel openers such as cromakalim and lemakalim, developed as antihypertensive drugs, are only weak bronchodilators because they activate ATP-sensitive K⁺ channels, whereas the most important effectors of airway smooth-muscle hyperpolarization and relaxation are the high-conductance, Ca²⁺-dependent K⁺ channels (maxi-K channels). The latter are positively modulated by some soya saponin extracts purified from *Desmodium adscendens*, a medicinal herb used by indigenous African populations to treat asthma, dysmenorrhea, and other diseases associated with dysfunction of smooth-muscle contractile responses (6).

Indeed, at present, β_2 -agonists, which activate maxi-K channels by both cAMP-dependent phosphorylation and direct stimulation operated by the G protein (Gs) coupled to β -adrenergic receptors, remain the most effective maxi-K channel openers. To our knowledge, in fact, selective powerful activators of these channels are not currently available.

Anticholinergic agents

Among the anticholinergic agents, selective drugs capable of blocking only certain subtypes of muscarinic receptors may provide a significant improvement with respect to the currently available, nonspecific antimuscarinics such as ipratropium and oxitropium bromide. Indeed, selective blockade of M₁ and M₃ receptors involved in the facilitation of ganglionic neurotransmission and bronchoconstriction, as well as mucus hypersecretion, respectively, would be very useful in the

absence of any interference with prejunctional M_2 autoreceptors, which inhibit acetylcholine release from postganglionic parasympathetic fibers. A selective M_3 antagonist (darifenacin or UK88525) and a mixed M_1/M_3 antagonist (revatropate or UK112166) are now under clinical development (7). Moreover, there is the imminent introduction of tiotropium bromide (8), a new long-acting drug that dissociates slowly from M_1 and M_3 receptor subtypes, but dissociates rapidly from M_2 receptors, thus having only a short-lived effect on acetylcholine release.

New pharmacologic strategies

At present, the efforts aimed at achieving a better control of, or even a cure for, asthma include several different new pharmacologic strategies, all sharing a common basic principle; that is, to develop drugs more directly targeted on the pathophysiology of the disease than those currently in use.

Leukotriene modifiers

Leukotriene modifiers have provided until now the only example of already marketed compounds that target specific steps in the asthmatic inflammatory process, unlike corticosteroids which exert a more general anti-inflammatory and immunosuppressive effect. In fact, cysteinyl leukotrienes (cysLTs) play a crucial role in almost all the pathologic features of asthma; namely, bronchoconstriction, mucosal edema, increased mucus secretion, eosinophil infiltration, and also airway remodeling (9). In this regard, it is noteworthy that glucocorticosteroids do not seem to modify *in vivo* leukotriene secretion significantly.

Currently approved leukotriene modifiers include cysLT₁ receptor antagonists (zafirlukast, montelukast, and pranlukast) and 5-lipoxygenase inhibitors (zileuton). These drugs are characterized by an interesting pharmacologic profile since they have both anti-inflammatory and bronchodilator properties (10). The precise placement of leukotriene modifiers in asthma therapy still needs to be defined. Present clinical evidence suggests that these agents, administered alone, may provide a valid option in the initial anti-inflammatory treatment of mild asthma, and their suitability is also owing to good patient compliance due to both the possibility of oral administration and the lack of significant side-effects. In moderate-to-severe asthma treatment, leukotriene modifiers, given in association with the traditional antiasthma drugs, may be able to exert significant steroid and β_2 -agonist sparing effects. Moreover, leukotriene modifiers now represent the first-line therapy for aspirin-induced asthma, a condition in which cysLTs play a pathophysiologic role of particular importance.

Tachykinin antagonists

Neurogenic airway inflammation may be successfully inhibited by the recently developed nonpeptide tachykinin antagonists (CP96345, FK224, and the long-acting and orally active LY303870), which have allowed us to overcome the problems associated with peptide antagonists, mainly due to rapid enzymatic degradation. Selective NK₁ or NK₂ as well as dual NK₁/NK₂ receptor antagonists are currently available; these drugs block the inflammatory effects of the neurokinins released into the airways by sensory nerve stimulation, thus inhibiting the increase in vascular permeability caused by substance P, and reducing the bronchial hyperresponsiveness experimentally induced by some stimuli (allergens and citric acid) (11).

Endothelin antagonists

Endothelin-1 (ET-1) is an important mediator of asthma that seems to exert its powerful bronchoconstrictive action through stimulation of ET_B receptors, densely expressed in both central and peripheral airways (12). Selective endothelin receptor antagonists are now available (e.g., BQ123 and BQ788) that display differential effects for ET_A and ET_B receptors and are suitable for clinical trials.

Adenosine receptor inhibitors

Compelling evidence suggests that adenosine induces bronchoconstriction via stimulation of A₁-receptors, which appear to be overexpressed in allergic rats and rabbits, as well as in asthmatic patients. Respirable antisense oligonucleotides (RASONS) have been designed which hybridize to A₁-receptor mRNA (EPI 2010 and EPI 2019), thereby impeding its template function and selectively reducing A₁-receptor number in the lung (13). Inhaled EPI 2010 is able to attenuate sensitivity to house-dust mite in allergic rabbits and is also effective in the *Ascaris*-sensitized primate model of experimental asthma. In addition to having the advantage of being directly deliverable to the airways, the RASON approach might be more efficient and specific than traditional antagonist drugs; therefore, it appears to be applicable to other protein targets involved in inflammatory responses.

Tryptase inhibitors

Tryptase, which is released from activated mast cells, induces eosinophil chemotaxis and activation as well as collagen type I synthesis by lung fibroblasts. *In vitro* studies and preclinical trials have shown that the antitryptase agents APC366 and BAY17, whose pharmacokinetic profile is probably suitable for both inhalant and oral routes, are quite effective in inhibiting early and late allergic asthmatic reactions (14).

Cytokine and chemokine inhibitors

Since many proinflammatory cytokines and chemokines play a central role in the pathophysiology of asthma, they represent very important targets for the development of new antiasthma treatments.

IL-5 inhibitors. A key target for therapeutic intervention in asthma is interleukin-5 (IL-5), which induces proliferation, differentiation, recruitment, and activation of eosinophils. Experimental strategies aimed at IL-5 inhibition may include synthesis of antisense oligonucleotides, utilization of anti-IL-5 monoclonal antibodies, and development of IL-5-receptor antagonists. It has been recently shown that a 16-base-long deoxyoligonucleotide construct, antisense to IL-5 mRNA, is able to induce a complete inhibition of IL-5 secretion by human peripheral blood mononuclear cells (15). An anti-IL-5 monoclonal antibody (SCH55700) has a powerful and durable inhibitory action on airway eosinophilia and hyperresponsiveness in allergic animal models. Such a prolonged effect suggests that this antibody acts by preventing activation and differentiation of bone-marrow eosinophil progenitors (16); clinical studies are underway. Moreover, the recent advances in the structural and functional characterization of the IL-5 receptor, particularly its α chain responsible for ligand binding, may lead to the development of potent and selective antagonists.

JAK-STAT inhibitors. It has been recently revealed that specific cellular responses induced by cytokines are mediated by a selective involvement of the various members of the JAK (Janus kinases)-STAT (signal transducers and activators of transcription) signal-transducing protein families. In Th2 cells, for example, transcriptional activation of the gene encoding IL-4, which is induced by IL-4 itself, is mediated by JAK1/3-dependent stimulation of STAT6. In fact, by specifically disrupting ("knocking out") the gene encoding STAT6, it is possible to produce mice which after allergen challenge show a remarkable decrease, in comparison with their wild-type littermates, in antigen-induced stimulation of IgE production, Th2 cytokine response, and airway hyperresponsiveness (17). Conversely, in Th1 cells, IL-12 regulates interferon-gamma (IFN- γ) gene expression by utilizing the JAK2-STAT4 signal-transducing pathway. Therefore, specific endogenous STAT inhibitors, which have been recently isolated and designated as SSI (STAT-induced STAT inhibitors), should provide a very useful tool with which to shut down the atopic response.

NF- κ B inhibitors. Inhibition of nuclear factor κ B (NF- κ B) represents a key strategy in asthma treatment. In

fact, this transcription factor is ubiquitously expressed in both inflammatory and structural airway cells, is activated by a wide variety of asthmatic stimuli, and regulates the synthesis of several different pro-inflammatory proteins (18) involved in asthma pathophysiology. The recently developed synthetic NF- κ B inhibitors SP650003 and SP100030 are capable of significantly attenuating NF- κ B/AP-1-dependent gene transcription. Furthermore, some naturally occurring NF- κ B inhibitors have also been identified, such as the *Aspergillus* derivative gliotoxin. Another approach is to target the specific kinases (I κ B kinases) that promote NF- κ B function via inactivation of its associated inhibitor I κ B, which, upon phosphorylation, undergoes rapid proteolysis (19). Peptide inhibitors of the I κ B kinases- α (IKK- α) and - β (IKK- β) are now available, and their therapeutic potential seems to be very interesting.

Anti-inflammatory cytokines. In addition to the pro-inflammatory cytokines implicated in asthma pathophysiology, there are also some anti-inflammatory cytokines (e.g., IL-10) and cytokines, such as IL-10, IL-12, IFN- γ , and IL-18, which may be able to interfere with the allergic response.

In regard to this approach, the therapeutic use of IL-10 is particularly promising because this cytokine inhibits IL-5 synthesis by Th2 cells, reduces the production of the eosinophilopoietic cytokines IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF), promotes eosinophil death, and also inactivates alveolar macrophages (20). At the molecular level, IL-10 seems to operate by inhibiting I κ B degradation, thus preventing activation of NF- κ B. The importance of the antiallergic function of IL-10 is confirmed by its reduced concentration in the BAL fluid of asthmatic patients, in comparison with normal subjects (21). Therefore, administration of exogenous IL-10 to asthmatic individuals may significantly help to restore the balance between proinflammatory and anti-inflammatory endogenous cytokines; clinical trials with IL-10 show an advantageous safety profile, thus suggesting a possible utilization by either systemic or topical routes.

IL-12 plays a crucial role in immune regulation by driving commitment from the T helper 0 (Th0) to the Th1 phenotype, modulating IgE synthesis, and promoting IFN- γ secretion (22). IL-12 by itself is ineffective in reconvertng an already established Th2 phenotype to a Th1 secretory pattern because Th2 cells lack the β_2 chain of the IL-12 receptor. However, recent data obtained using a mouse model of allergic asthma indicate that coadministration of IL-12 and IL-18, a cytokine that synergizes with IL-12, prevents, unlike either IL-12 or IL-18 used alone, antigen-induced full differentiation of Th2-like cells, IgE upregulation,

eosinophil infiltration, and airway hyperresponsiveness (23).

Chemokine receptor antagonists. Chemokines (CXC, CC, CX₃C, and C chemokines) play a key role in inflammation and immune response by regulating the traffic of granulocytes and lymphocytes. Several CC chemokines (β -chemokines), such as eotaxin, RANTES (regulated on activation normal T-cell expressed and secreted), macrophage inflammatory protein 1 α (MIP-1 α), and the monocyte chemoattractant peptides 1, 2, 3, and 4 (MCP-1, -2, -3, and -4), are important effectors of the selective recruitment and activation of eosinophils, basophils, and Th cells, thus representing another suitable target for drug intervention. It is now well established that chemokines exert their powerful chemoattractant effects by interacting with many different G protein-coupled receptors (CCR1-CCR9, CXCR1-CXCR5, and CX₃CR1). Interestingly, these receptors are differentially expressed on the various cell types since eosinophils express CCR1 and CCR3, basophils CCR3 and CCR4, and Th2 cells CCR3 and CCR4, whereas CXCR3 are restricted to Th1 cells (24). Therefore, the development of specific CCR3 antagonists affecting eosinophil, basophil, and Th2, but not Th1, cell recruitment may open a very promising new line of antiasthma therapy. Receptor antagonists have been engineered by modifying the N-terminal region of chemokines, thus producing potent molecules such as MetRANTES, which retains the initiating methionine, and which has been successfully used to inhibit experimental lung inflammation (24).

Direct inhibitors of T-cell function

Besides the inhibition of Th2 activation by blocking either the synthesis or action of specific cytokines and chemokines, it is also possible to interfere with T-cell function by other strategies. For example, anti-CD4⁺ antibodies may be utilized, and one of these (SB210396) is undergoing clinical trials, with apparently encouraging preliminary results (25).

Alternatively, programmed cell death (apoptosis) may be exploited for therapeutic purposes with the goal of reducing Th2 expansion. Apoptosis of T cells is predominantly mediated by the interaction of Fas/APO-1, a 45-kDa membrane protein belonging to the tumor necrosis factor receptor family, and its ligand FasL. Recent studies have demonstrated that Fas is hypoexpressed on pulmonary T cells from asthmatic patients, in comparison with normal subjects, thus suggesting that the related reduction of T-cell apoptosis significantly contributes to the persistence of airway inflammatory infiltrates in asthma (26). Therefore, Th2 expansion could be limited or even blocked by

therapeutically restoring apoptosis, as, for example, through administration of Fas-activating antibodies (27). T-cell apoptosis might also be achieved in a Fas-independent manner by pharmacologically manipulating the interaction between the costimulatory molecule B7 expressed on antigen-presenting cells and its counterreceptor CD28 located on the T-cell surface. In fact, in addition to providing a costimulatory signal required for antigen-driven activation of resting T cells, B7-CD28 interaction is also involved in triggering an apoptotic program in preactivated T cells (activation-induced cell death), thus serving as a regulatory mechanism which limits the immune response to specific antigens.

Another hypothetical therapeutic approach may consist in targeting the nuclear transcription factors responsible for IL-4-induced Th2 differentiation and activation. These include the proto-oncogene product *cMaf*, which specifically activates the IL-4 gene, activator protein 1 (AP-1), and the zinc finger DNA-binding protein GATA-3, which appear to be involved in the transcriptional regulation of almost all the genes associated with the Th2 phenotype.

Adhesion molecule blockers

Airway infiltration by inflammatory cells depends on their adhesion to the vascular endothelium and the subsequent migration into the bronchial wall. These processes require the expression on leukocytes, endothelial and epithelial cells, and even smooth-muscle cells, of several different families of glycoprotein adhesion molecules, which represent another target for antiasthma therapies.

Among adhesion molecules, one of the most specific therapeutic targets is very late antigen-4 (VLA-4), an $\alpha_4\beta_1$ integrin expressed on eosinophils, T cells, monocytes, and mast cells, but not neutrophils, which acts as a counterreceptor for vascular adhesion molecule-1 (VCAM-1). Recent studies have shown that monoclonal antibodies against VLA-4 as well as small molecule VLA-4 inhibitors (CY9652, BI01211) (28), given by aerosol, protect against antigen-induced late responses and airway hyperresponsiveness in allergic sheep. Also developed have been other small molecule inhibitors (PD144795) that operate at the level of gene transcription, thereby inhibiting the expression of various adhesion molecules such as VCAM-1, ICAM-1, and E-selectin.

New immunotherapeutic approaches

Conventional immunotherapy for atopic diseases, based on allergen desensitization, has several limitations because it may induce anaphylactic reactions, it is targeted only on specific allergens, its precise mechanism of action is poorly defined, and its real effectiveness

is still questioned. Therefore, new experimental forms of immunotherapy are now emerging, such as anti-IgE therapies, gene vaccination with plasmid DNA, and administration of immunogenic mycobacterial preparations.

Anti-IgE therapies

IgE antibodies play a central role in the induction and maintenance of allergic inflammation by interacting with high-affinity IgE receptors (Fc ϵ RI), located on mast cells, basophils, and dendritic cells, and low-affinity IgE receptors (Fc ϵ R2/CD23) expressed on B cells, monocyte/macrophages, and eosinophils, thus triggering the release of multiple mediators and cytokines as well as enhancing antigen presentation.

The most promising anti-IgE approach now appears to be represented by specific antibodies directed against the IgE region involved in Fc ϵ RI binding, which are effectively able to inhibit the interaction between IgE and their receptors on inflammatory cells (29, 30). These anti-IgE antibodies are "nonanaphylactogenic" because they do not induce IgE receptor cross-linking and mediator release, thus having a very interesting therapeutic potential and a good safety profile. Since the binding site for Fc ϵ R2 is probably located on the same IgE domain responsible for the interaction with Fc ϵ RI, nonanaphylactogenic anti-IgE antibodies can block effector functions mediated by both high-affinity and low-affinity IgE receptors. Such antibodies, in addition to inhibiting activation of IgE-sensitized mast cells and basophils, are also able to suppress new IgE formation, probably by neutralizing the interaction of IgE with the Fc ϵ R2 located on IgE-switched B cells.

In vivo studies, also including clinical trials, have shown that systemic administration of nonanaphylactogenic anti-IgE antibodies is well tolerated and causes an impressive decrease in free serum IgE levels, a significant attenuation of both early- and late-phase asthmatic responses, and a remarkable inhibition of antigen-induced bronchial hyperresponsiveness and pulmonary eosinophil infiltration, as well as a marked reduction of eosinophilia in induced sputum.

Gene vaccination with plasmid DNA

A very attractive new immunotherapeutic strategy is gene vaccination, which allows us to blunt the allergic inflammatory process through the intramuscular injection of bacterial plasmid DNA encoding a specific antigen. Such a modality promotes an immune deviation of the predominant Th2 response occurring in asthma to the Th1 phenotype. This effect is due to the induction of both IL-12 and IFN- γ , which is also the presumptive mechanism of action of conventional immunotherapy. In comparison with the latter, however, plasmid DNA immunization is significantly more advantageous because only very small quantities of

allergens are produced; therefore, the risk of anaphylactic reactions is almost absent. Furthermore, the allergen gene can be manipulated in order to make a construct that contains the immunostimulatory nucleotide sequence (ISS) of the plasmid DNA. ISS includes the CpG motif (cytosine and guanidine base pairs), thought to be responsible for stimulation of IL-12 and IFN- γ , which is present in bacterial plasmids at a much higher amount than in mammalian DNA. It has been shown in animal models of asthma that gene vaccination elicits a sharp fall in total and specific IgE levels and also reduces antigen-induced eosinophilic lung infiltration (31); this fascinating novel approach is now undergoing clinical trials and appears to be suitable for application in the immunotherapy of allergic asthma.

Mycobacterial preparations

Bacillus Calmette-Guérin (BCG) vaccine, an attenuated form of *Mycobacterium bovis* containing the CpG-oligonucleotide immunostimulatory sequence, seems to be able, in mice, to suppress antigen-induced airway eosinophilia and to reduce the levels of IL-4 and IL-5 in BAL fluid (32). These effects are concomitant with an increased release of IFN- γ , which mediates a shift in the immune response from a Th2 pattern to a Th1 secretory profile. Similar, though not identical results have been obtained with a killed preparation of *M. vaccae* (33), which is now under clinical trial. Such data may confirm the hypothesis that the increase in asthma prevalence and incidence occurring in the "Westernized" world is attributable to a relatively unopposed Th2 stimulation, presumably due to a defective Th1 response caused by the sharp decline in the incidence of tuberculosis and other infectious diseases.

Conclusion

The recent advances in the knowledge of the pathophysiology of asthma have led to a significant expansion of the experimentally available treatment options, some of which will probably come into clinical application in the near future. These new therapeutic approaches have the advantage, in comparison with the currently used anti-inflammatory and immunosuppressive drugs such as corticosteroids, of being more specifically targeted on the pathogenetic events involved in asthma, thus, theoretically, giving the opportunity to realize an optimal control of the disease without impairing the global effectiveness of immune response.

A further contribution to asthma therapy may come from genetic studies. Since the asthma phenotype probably depends upon the interaction of environmental factors with a complex combination of multiple gene abnormalities (polygenic disease) (34), rather than on a single major genetic defect, gene therapy strategies do not appear to be practicable at the present time.

However, a better knowledge of asthma genetics may open exciting new therapeutic perspectives, thus promoting the design of drugs capable of either directly modulating relevant genes or targeting their protein

products. Therefore, the application of genetics to pharmacology (pharmacogenetics) may eventually lead in the next decades to the development of a definitive cure for this widespread disease.

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