NEW DRUGS FOR ASTHMA

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Abstract | Asthma is a major and increasing global health problem and, despite major advances in therapy, many patients' symptoms are not adequately controlled. Treatment with combination inhalers, which contain a corticosteroid and long-acting β_2 adrenoceptor agonist, is the most effective current therapy. There is therefore a search for new therapies, particularly safe and effective oral treatments and those that are more efficacious in severe asthma. New therapies in development include mediator antagonists and inhibitors of cytokines, although these therapies might be too specific to be very effective. New anti-inflammatory therapies include corticosteroids and inhibitors of phosphodiesterase-4, p38 mitogen-activated protein kinase and nuclear factor-κB. The prospects for a curative treatment are on the horizon.

T_H2 CELL
T helper 2 lymhocytes that predominate in asthma and which are characterized by the production of interleukins 4, 5, 9 and 13.

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Despite considerable effort by the pharmaceutical industry, it has proved very difficult to develop new classes of therapeutic agents for asthma. This is partly because existing drugs are effective and safe, and partly because animal models of asthma are poor and do not seem to be predictive of clinical efficacy. The current worldwide asthma market exceeds US $4 billion and is increasing rapidly[1], which reflects the enormous increase in prevalence of asthma and the increasing recognition that chronic anti-inflammatory treatment is needed for many patients. In addition, despite the availability of effective and relatively cheap treatments, approximately 5% of asthmatic patients remain poorly controlled. Current therapy is shown in TABLE 1. Compliance with inhaled therapy, particularly corticosteroids, is poor and might be improved with oral therapy given once daily. Yet oral therapy presents the problem of systemic side effects. This necessitates the development of oral drugs to *specifically* treat asthma that do not have effects on normal physiological mechanisms (unlike β-adrenoceptor agonists and corticosteroids).

Asthma is characterized by a specific pattern of inflammation in the airway mucosa, and involves the infiltration of eosinophils, increased numbers of T_H2 cells relative to T_H1 cells, and increased numbers of activated mast cells[2,3]. In addition, there are characteristic structural changes to the airways (termed remodelling), some of which might even precede the development of the disease. These changes include subepithelial fibrosis (basement membrane thickening), airway smooth muscle hypertrophy and hyperplasia, angiogenesis and increased mucus secretory cells (goblet-cell hyperplasia and submucosal-gland hyperplasia)[4]. Neural mechanisms are also important in asthma, such as the sensitization of sensory nerve endings in the airways and reflex effects on airway tone. Asthma is a highly complex disease (FIG. 1) that involves many inflammatory cells, mediators and inflammatory proteins, and therefore treatments that target a single cell or mediator are unlikely to be effective.

There are three major approaches for asthma drug development: improvements in existing classes of effective drug; the development of novel compounds; and the development of novel compounds based on serendipity — for example, from other disease areas. Only the first two approaches have been adopted so far. Improvements in corticosteroids (improved pharmacokinetics) and β_2-adrenoceptor agonists (longer duration of action) have been made, but most drugs in development represent approaches based on a better understanding of the underlying inflammatory and immune mechanisms of asthma.

New corticosteroids

The currently available inhaled corticosteroids are all absorbed from the lungs into the systemic circulation, and therefore have the potential for systemic side

Table 1 | **Current therapies used in asthma**

Bronchodilators	Anti-inflammatory therapies
Inhaled short-acting β_2-agonists: salbutamol and terbutaline	Inhaled corticosteroids: budesonide, fluticasone propionate, beclomethasone dipropionate and mometasone
Inhaled long-acting β_2-agonists: salmeterol and formoterol	Antileukotrienes: montelukast, pranlukast and zafirlukast
Inhaled anticholinergics: ipratropium bromide and tiotropium bromide	Cromones: sodium cromoglycate and nedocromil sodium
Theophylline: slow-release theophylline and aminophylline	Anti-immunoglobulin E: omalizumab

effects when administered at high doses[5,6]. To circumvent this issue, some innovative variations of corticosteroids have been tried and tested.

Soft steroids and ciclesonide. Soft steroids are corticosteroids that are inactivated by esterases in the airways, so that any corticosteroid not taken into airway cells is not available for systemic absorption. However, soft steroids such as butixocort and tipredane were ineffective in clinical studies in asthma[7], possibly because they were inactivated before they were able to enter target cells in the airways. In a similar approach, ciclesonide, an inactive prodrug, liberates the active desisobutyryl-ciclesonide in response to esterases in the airways[8]. Ciclesonide has anti-inflammatory effects[9] and its extended lung-retention time means that it is effective after once-daily inhalation in asthmatic patients.

Dissociated corticosteroids. A major mechanism of the anti-inflammatory effect of corticosteroids seems to be inhibition of the effects of pro-inflammatory transcription factors that are activated by pro-inflammatory CYTOKINES via an inhibitory action (transrepression) on histone acetylation and stimulation of histone deacetylation[10]. By contrast, the systemic side effects of corticosteroids are likely to be mediated predominantly via DNA binding (transactivation)[11]. Novel corticosteroids that could selectively transrepress pro-inflammatory genes without significant transactivation of genes involved in the metabolic effects of corticosteroids would therefore be desirable. The separation of transactivation and transrepression has been demonstrated with reporter gene constructs in transfected cells using selective mutations of the glucocorticoid receptor[12]. Indeed, the topical steroids fluticasone propionate and budesonide seem to have more potent transrepression than transactivation effects, which could account for their profile as potent anti-inflammatory agents[13].

Dissociated steroids, including RU24858 and RU40066, have anti-inflammatory effects *in vitro*[14], although there is little separation of anti-inflammatory effects and systemic side effects *in vivo*[15]. However, novel dissociated corticosteroids are now in clinical development and show good separation between transrepression and transactivation activities *in vivo*[11]. Structural characterization of the ligand-binding domain of the glucocorticoid receptor should aid the design of improved dissociated steroids[16].

CYTOKINE
A small protein mediator that acts as a communicator between cells.

BRONCHODILATOR
A drug that relaxes airway smooth muscle and provides immediate relief from asthma symptoms.

AIRWAY HYPERRESPONSIVENESS (AHR). Exaggerated airway-narrowing response to many environmental triggers, such as allergen and exercise, which is characteristic of asthma. It is normally measured by histamine or methacholine challenge.

New bronchodilators

Although several novel classes of BRONCHODILATOR have now been explored, it is difficult to find a drug class of comparable efficacy and safety to the β_2-adrenoceptor agonists which also counteracts all known bronchoconstrictor mechanisms. Several new β_2-adrenoceptor agonists with a long duration of action that will be suitable for once-daily administration are now being tested, and are likely to become the bronchodilators of choice in the future when used in combination inhalers with a long-acting corticosteroid. Several novel bronchodilators have been developed on the basis of knowledge of the mechanism of action of β_2-adrenoceptor agonists (FIG. 2).

Vasoactive intestinal peptide. Vasoactive intestinal peptide (VIP) is a potent relaxant of constricted human airways *in vitro*, but its degradation in airway epithelium means that it is ineffective in asthmatic patients[17]. A more stable cyclic analogue of VIP (Ro-25-1553) has a more prolonged effect *in vitro* and *in vivo* and is effective in asthmatic patients by inhalation[18].

Prostaglandin E_2. Although prostaglandin E_2 (PGE_2) relaxes airways *in vitro* and is involved in the refractory response of the airways to exercise[28], it is not effective as a bronchodilator *in vivo*, and can even lead to constriction and coughing in asthmatics through stimulation of sensory nerves in airways. PGE agonists that are selective for receptor subtypes could avoid the problem of coughing and might be worthy of further exploration as bronchodilator/anti-inflammatory drugs[27].

Atrial natriuretic peptide. Intravenous infusion of atrial natriuretic peptide (ANP) produces a significant bronchodilator response and protects against bronchoconstriction induced by inhaled bronchoconstrictors such as methacholine[19]. Although ANP itself is susceptible to enzymatic breakdown, it is possible that non-peptide agonists of ANP receptors could be developed in the future. The related peptide urodilatin (ularitide) has a longer duration of action than ANP, is less susceptible to degradation and is as potent as salbutamol when intravenously infused in asthmatic subjects[20].

K^+ channel openers. Drugs that selectively open an ATP-dependent K^+ channel (K^+ channel openers (KCOs)), such as levcromakalim, are effective bronchodilators of human airways *in vitro*, but are ineffective *in vivo* at maximally tolerated oral doses[21]. KCOs might also be effective as inhibitors of sensory nerve activation, and therefore could be useful in inhibiting cough and AIRWAY HYPERRESPONSIVENESS (AHR)[22]. Several KCOs have been studied in Phase I/II trials, but their development for asthma was halted because of dose-limiting vasodilator side effects (headaches and postural hypotension).

Mediator antagonists

Antihistamines. Although classical antagonists of the H_1 receptor are of little clinical value in asthma[23], the recent discovery of H_4 receptors expressed on mast cells, T cells and eosinophils has raised the possibility that H_4 receptor

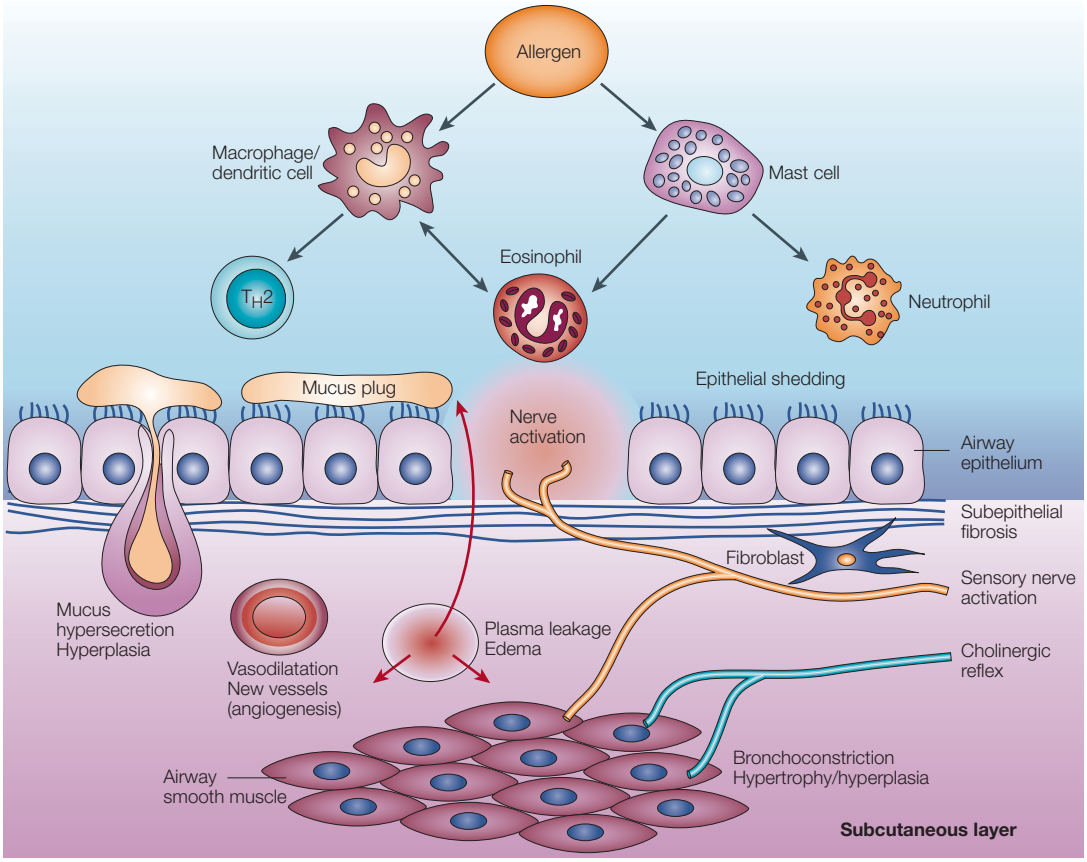

Figure 1 | **The pathophysiology of asthma.** Several inflammatory cells are recruited and/or activated in the airways, releasing a variety of inflammatory mediators that have acute effects on the airway (such as bronchoconstriction, plasma leakage, vasodilatation, mucus secretion, sensory nerve activation and cholinergic reflex-induced bronchoconstriction), together with structural changes (remodelling) that include subepithelial fibrosis, increased numbers of blood vessels and mucus-secreting cells, and increased thickness of airway smooth muscle as a result of hyperplasia and hypertrophy.

antagonists could be beneficial in asthma[24]. The selective H_4 receptor antagonist JNJ 7777120 potently inhibits mast-cell activation and chemotaxis, and might therefore be of potential benefit in reducing asthma symptoms and exacerbations[25].

Leukotriene modifiers. Leukotriene modifiers, including antileukotrienes (for example, montelukast, pranlukast and zafirlukast) and 5-lipoxygenase (5-LO) inhibitors (zileuton), were, 5 years ago, the first new class of anti-asthma treatment to be introduced in 30 years[26]. Although antileukotrienes have had some clinical success in asthma, they are considerably less effective and more expensive than inhaled corticosteroids[27]. Current antileukotrienes are potent and selective competitive antagonists of the leukotriene $CysLT_1$ receptor, which mediates bronchoconstriction, plasma exudation and mucus secretion; however, a second receptor, termed $CysLT_2$, might also be an important target for asthma, because it mediates some responses to CysLTs, such as airway smooth-muscle-cell proliferation[28].

Zileuton is a relatively weak 5-LO inhibitor, and has a short duration of action. However, in terms of clinical efficacy it is similar to the more potent antileukotrienes, which perhaps indicates that more potent 5-LO inhibitors might be more effective clinically. 5-LO inhibitors block the generation of CysLTs, but also of the leukotriene LTB_4 receptor, which might have a role in more severe asthma. However, LTB_4 receptor antagonists (BLT_1 antagonists) do not inhibit allergen-induced responses in asthmatic patients[29]. The development of 5-LO inhibitors has been limited by liver toxicity, and although inhibitors of 5-LO-activating protein (FLAP) seem to be less toxic, they lacked efficacy in clinical studies[30].

Prostaglandin antagonists. Deletion of prostaglandin D_2 (PGD_2) receptors in mice significantly inhibits inflammatory responses to allergen and AHR, which indicates that PGD_2 might be important in asthma[31]. PGD_2 activates the chemoattractant receptor of T_H2 cells ($CRTH_2$), which is expressed on T_H2 cells, eosinophils and basophils, and which mediates the chemotaxis of these cell types — thereby providing a possible link between mast-cell activation and allergic inflammation[32]. However, blocking the production of PGD_2 with cyclooxygenase inhibitors has not been beneficial in asthma.

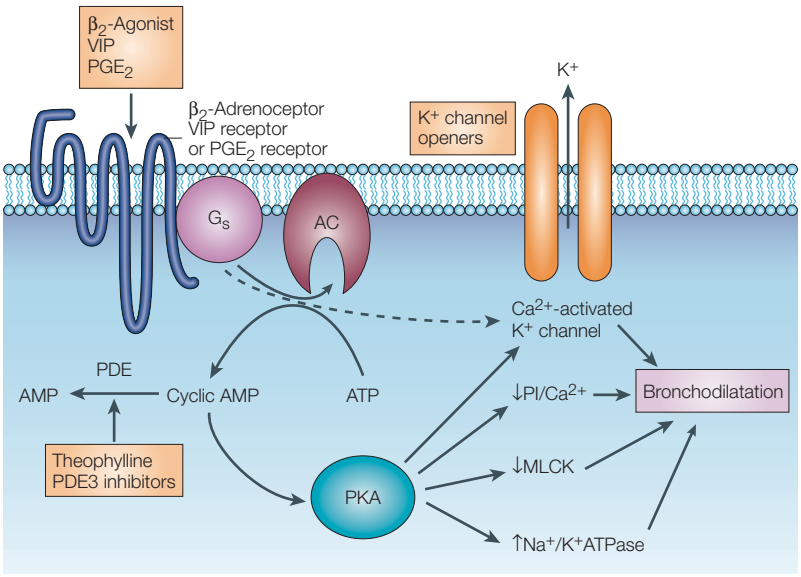

Figure 2 | **Molecular mechanisms of action of bronchodilators.** Activation of β_2 adrenoceptors, vasoactive intestinal peptide (VIP) and prostaglandin E_2 (PGE_2) receptors results in activation of adenylyl cyclase (AC) via a stimulatory G-protein (G_s) and an increase in cAMP concentration. This activates protein kinase A (PKA), which then phosphorylates several target proteins, resulting in the opening of calcium-activated potassium channels (K_{Ca}) or maxi-K channels, decreased phosphoinositide (PI) hydrolysis, increased Na^+/K^+ ATPase and decreased myosin light chain kinase (MLCK) activity, which leads to relaxation of airway smooth muscle. In addition, β_2-adrenoceptors can be coupled directly via G_s to K_{Ca}. cAMP is broken down by phosphodiesterases (PDE), which are inhibited by theophylline and selective PDE3 inhibitors, and which could therefore be potential asthma therapies.

Endothelin antagonists. Endothelin-1 (ET1) induces airway smooth-muscle-cell proliferation and promotes a pro-fibrotic phenotype, and might therefore have a role in chronic inflammation and airway remodelling in asthma. Several potent antagonists of endothelin receptors have been developed[33], but because both ET_A and ET_B receptors might be involved in bronchoconstriction and structural changes in asthma, the development of non-selective antagonists would be preferable. However, it would be difficult to detect the effect of a drug on slow remodelling processes in the absence of validated biomarkers.

Nitric oxide inhibitors. The concentration of nitric oxide (NO) in the exhaled air of asthma patients is higher than that of normal subjects[34], probably as a result of increased inducible NO synthase (iNOS) expression in airway epithelial cells and infiltrating inflammatory cells[35,36]. An inhibitor of iNOS might therefore be useful in the treatment of asthma, particularly for restoring steroid responsiveness in patients with severe disease. Several potent and long-lasting iNOS inhibitors are now in development. For example, the prodrug L-N^6-(1-iminoethyl)lysine-5-tetrazole amide (SC-51), which is rapidly converted *in vivo* to the active metabolite L-N^6-(1-iminoethyl)lysine (L-NIL), markedly reduces the levels of exhaled NO in asthmatic patients for several days after oral administration[37].

Adenosine antagonists. Adenosine seems to activate mast cells via adenosine A_{2B} receptors; antagonists of this receptor might therefore be of value in asthma, although it has been difficult to identify compounds that selectively target this receptor[38]. Conversely, adenosine itself has an inhibitory effect on granulocytes, including eosinophils, and this action is mediated via adenosine A_{2A} receptors[39]; several selective A_{2A} agonists are currently in development, such as CGS 21680, which inhibits allergic inflammation in rats[40]. ATP also enhances the release of mediators from sensitized human mast cells via the $P2Y_2$ receptor that is expressed on eosinophils[41], indicating that $P2Y_2$ antagonists might also be beneficial in the treatment of asthma[42].

Tryptase inhibitors. Mast-cell tryptase increases the responsiveness of airway smooth muscle to constrictors, increases plasma exudation, potentiates eosinophil recruitment and stimulates fibroblast and airway smooth-muscle proliferation[43]. Some of these effects are mediated by activation of the protease-activated receptor PAR2, which is widely expressed in the airways of asthmatic patients[44]. The tryptase inhibitor APC366 is effective in a sheep model of allergen-induced asthma[45], but is only poorly effective in asthmatic patients[46]. Selective tryptase inhibitors with greater potency and selectivity are currently in development[47]; for example, BMS-363131 has nanomolar potency and is 3,000-fold more selective for tryptase compared with other serine proteases[48].

There are several possible approaches to inhibiting specific pro-inflammatory cytokines, which are summarized in FIG. 3. Conversely, some cytokines that suppress the allergic inflammatory process might themselves have therapeutic potential in asthma[49,50].

Interleukin inhibitors

Interleukin-5 (IL-5) is essential in orchestrating the eosinophilic inflammation of asthma (FIG. 4)[51]. The eosinophilic response to allergen in IL-5 gene knockout mice, and subsequent AHR, are markedly suppressed, and yet animals have a normal survival. Blockage of IL-5 has also been achieved using antibodies, and inhibits eosinophilic inflammation and AHR in primate models of asthma[51]. Humanized monoclonal antibodies to IL-5 have been developed, and a single intravenous infusion of one of these antibodies (mepolizumab; GlaxoSmithKline) markedly reduces blood eosinophils for more than 3 months and prevents eosinophil recruitment to the airways after allergen challenge in patients with mild asthma[52]. However, this treatment has no significant effect on the early or late response to allergen challenge or on baseline AHR, which indicates that eosinophils might not be of crucial importance for these responses in humans. Indeed, a clinical study of an anti-IL-5 antibody in patients with moderate to severe asthma that was not controlled by inhaled corticosteroids confirmed a reduction in circulating eosinophils, but no significant improvement in either asthma symptoms or lung function[53]. In both of these studies it would be expected that high doses of corticosteroids would improve these functional parameters. These surprising results raise doubts about the supposedly crucial role of eosinophils in asthma and indicate that other strategies aimed at

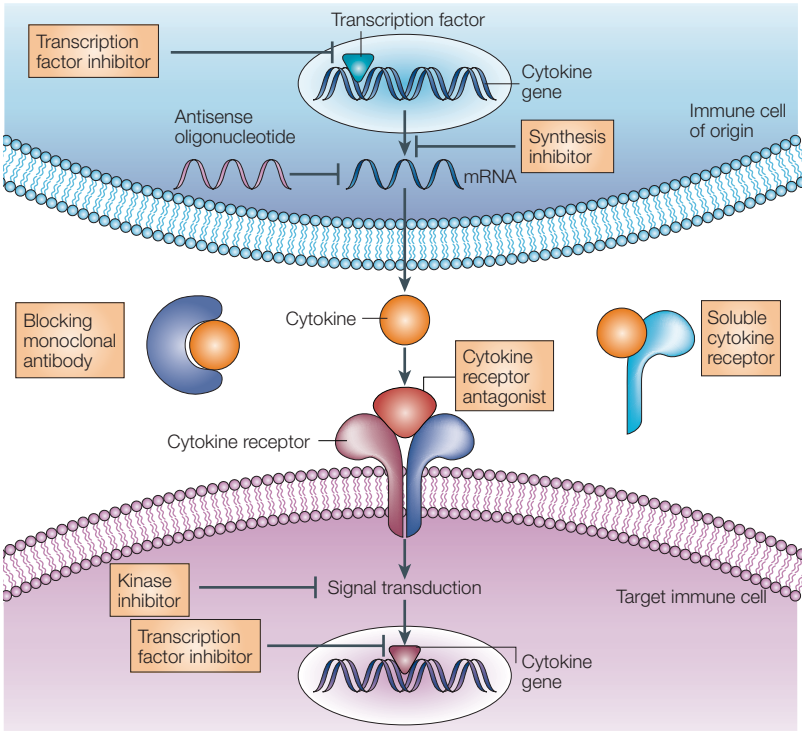

Figure 3 | **There are several strategies for inhibiting pro-inflammatory cytokines in asthma.** These include inhibition of cytokine synthesis (for example, corticosteroids), inhibition of transcription factors regulating cytokine expression (for example, calcineurin inhibitors or decoy oligonucleotides), inhibition of secreted cytokines with blocking antibodies (for example, anti-interleukin (IL)-5 antibody) or soluble receptors (for example, soluble IL-4 receptors), blocking cytokine receptors (for example, chemokine receptor antagonists), blocking signal-transduction pathways (for example, p38 mitogen-activated protein kinase inhibitors) or transcription factors activated by cytokines (for example, STAT6 inhibitors).

inhibiting eosinophilic inflammation might not be effective. However, although mepolizumab reduces circulating eosinophils by more than 95%, it is less effective at reducing eosinophils in bronchial biopsies (~50%), which might explain its lack of clinical efficacy[54]. Nevertheless, this indicates that blocking IL-5 itself is unlikely to be useful as an anti-asthma strategy.

Non-peptidic antagonists of the IL-5 receptor would be an alternative strategy, and would have the potential advantage of allowing oral administration. Molecular modelling of the IL-5 receptor α-chain and large-scale, high-throughput screening was used to discover YM-90709, a relatively selective inhibitor of IL-5 receptors[55]. However, the lack of clinical benefit of anti-IL-5 antibodies makes this a less attractive approach.

As well as its involvement in eosinophil recruitment to the airways[56], a unique function of IL-4 is to promote differentiation of T_H2 cells, acting at a proximal and crucial point in the allergic response. IL-4-blocking antibodies inhibit allergen-induced AHR, goblet-cell metaplasia and pulmonary eosinophilia in a murine model of asthma[57]. A single nebulized dose of soluble humanized IL-4 receptor (sIL-4r) prevents the fall in lung function induced by withdrawal of inhaled corticosteroids in patients with moderately severe asthma[58], and weekly nebulization improves asthma control[59]. Subsequent studies in patients with milder asthma proved disappointing, however, and this treatment has now been withdrawn. Recently, a heterodimeric soluble receptor containing each component of the IL-4 receptor (termed cytokine trap) has been shown to have a much higher affinity for IL-4, and might therefore be more useful[60]. Another approach is to use a mutated form of IL-4 (BAY 36-1677) that binds to and blocks the IL-4 receptor and IL-13 receptor α1, thereby blocking both IL-4 and IL-13 actions[61]. However, this treatment has a short duration of action.

IL-4 and the closely related cytokine IL-13 signal through a shared surface receptor, IL-4Rα, which activates the transcription factor STAT6 (REF. 62). Deletion of the gene encoding STAT6 has a similar effect to IL-4 gene knockout[63]. This has led to a search for inhibitors of STAT6, and although peptide inhibitors that interfere with the interaction between STAT6 and Janus-activated kinases linked to IL-4Rα have been discovered, it will be difficult to deliver these intracellularly, and therefore small-molecule inhibitors are being sought through screening efforts.

There is increasing evidence that IL-13 causes features in animal models that mimic asthma, including AHR, mucus hypersecretion and airway fibrosis, independently of eosinophilic inflammation[64] (FIG. 5). It potently induces the secretion of eotaxin from airway epithelial cells and transforms airway epithelium into a secretory phenotype. Knocking out the gene encoding IL-13 in mice, but not IL-4, prevents the development of AHR after allergen challenge, despite a vigorous eosinophilic response[65], and the increase in AHR induced by IL-13 is only seen when the expression of STAT6 is lost in airway epithelial cells[66]. IL-13 signals through IL-4Rα, but might also activate different intracellular pathways via activation of IL-13Rα1 (REF. 62), and its broad spectrum of effects makes it an important potential target for the development of new therapies.

A second specific IL-13 receptor, IL-13Rα2, exists in soluble form and has a high affinity for IL-13, thereby acting as a decoy receptor for secreted IL-13. Soluble IL-13Rα2 is effective in blocking the actions of IL-13, including IgE generation, pulmonary eosinophilia and AHR in mice[67]. In the murine asthma model, soluble IL-13Rα2 is more effective than IL-4-blocking antibodies, which highlights the potential importance of IL-13 as a mediator of allergic inflammation. Blocking IL-13 might be more important in established asthma, in which the concentration of IL-13 is much higher than that of IL-4. Humanized IL-13Rα2 and anti-IL-13 antibodies are now in clinical development as therapeutic approaches for asthma.

IL-9 is a T_H2 cytokine that enhances T_H2-driven inflammation, amplifies mast-cell mediator release and IgE production[68], and enhances mucus hypersecretion[69]. IL-9 and its receptors show an increased expression in asthmatic airways[70]; correspondingly, a blocking antibody to IL-9 inhibits airway inflammation and AHR in a murine model of asthma[71]. Strategies to block IL-9, including the use of humanized blocking antibodies, are now in development[72].

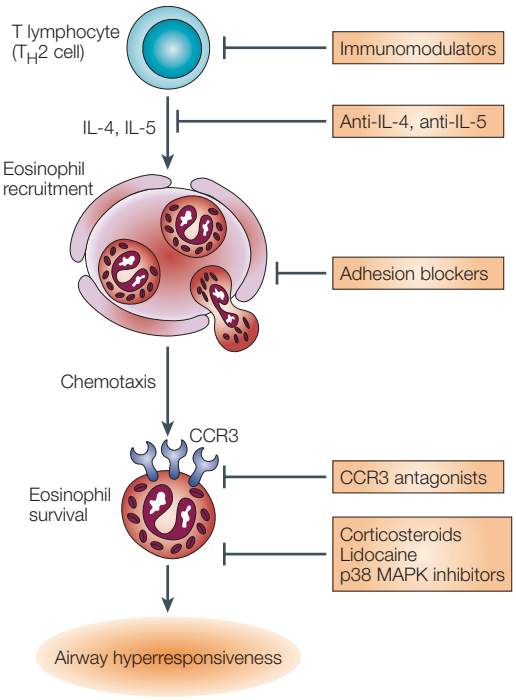

Figure 4 | **Inhibition of eosinophilic inflammation.** Several strategies are possible for the inhibition of eosinophil inflammation in tissues, including immunomodulators (for example, CyA, tacrolimus, rapamycin, mycophenolate, brequinar and suplatast tosylate), inhibitors of pro-inflammatory cytokines (for example, interleukin (IL)-4 and IL-5), inhibition of crucial adhesion molecules (for example, very late antigen-4, selectins, intercellular adhesion molecule-1), blockade of chemokine receptors on eosinophils (for example, chemokine receptor-3 (CCR3)) and induction of apoptosis by corticosteroids, lidocaine and p38 mitogen-activated protein kinase (MAPK) inhibitors.

IL-1 expression is increased in asthmatic airways[73] and activates many inflammatory genes that are expressed in asthma. There are no small-molecule inhibitors of IL-1, but the endogenous cytokine IL-1 receptor antagonist (IL-1ra)[74] was shown to reduce AHR induced by allergen in animal models. Human recombinant IL-1ra (anakinra (Kineret; Amgen)) does not seem to be effective, however[75].

TNF-α inhibitors

TNF-α is expressed in asthmatic airways and might be a key factor in amplifying asthmatic inflammation, through the activation of nuclear factor-κB (NF-κB), activator protein-1 (AP-1) and other transcription factors[76]. In rheumatoid arthritis and Crohn's disease, humanized monoclonal antibodies to TNF-α (for example, infliximab (Remicade; Centocor)) and soluble TNF-α receptors (for example, etanercept (Enbrel; Wyeth)) have produced remarkable clinical responses, even in patients who are relatively unresponsive to steroids[77]. TNF-α inhibitors are therefore a logical approach to asthma therapy, and clinical trials are now underway. However, there are some concerns about potential long-term adverse effects, such as increased susceptibility to infections. Because antibody-based therapies have to be given by injection, small-molecule inhibitors of TNF-α would be beneficial as they can be given orally. TNF-α-converting enzyme (TACE) is a matrix metalloprotease-related enzyme that is crucial for the release of TNF-α from the cell surface. Small-molecule TACE inhibitors are in development as oral TNF-α inhibitors, but cell-associated TNF-α might exert residual effects[78].

Cytokines as asthma drugs

Although it might not be feasible or cost-effective to administer anti-inflammatory cytokines[75,76] as a long-term therapy, it might in the future be possible to develop drugs that increase the release of these endogenous cytokines or activate their receptors and specific signal-transduction pathways.

IL-10 inhibits the synthesis of many inflammatory proteins that are overexpressed in asthma[79]. Indeed, there might be a defect in IL-10 transcription and secretion from macrophages in asthma, which indicates that IL-10 might be defective in atopic diseases[80,81]. In sensitized animals, IL-10 is effective in suppressing the inflammatory response to allergen[82], and cells that carry the CD4 antigen engineered to secrete IL-10 suppress airway inflammation in a murine model of asthma[83]. Specific allergen immunotherapy results in increased production of IL-10 by a subpopulation of regulatory T_H cells that are thought to mediate the beneficial effects of such immunotherapy[84]. Recombinant human IL-10 has proved to be effective in controlling Crohn's disease and psoriasis, a disease in which similar cytokines are expressed, and can be given as a weekly injection[85]. In mice, drugs that elevate cyclic AMP increase IL-10 production, but this does not seem to be the case in human cells[86].

Interferon (IFN)-γ inhibits T_H2 cells and should therefore reduce atopic inflammation by blocking the release of IL-5, which drives eosinophilia, and of IL-4 and IL-13, which induce immunoglobulin E (IgE) formation[87]. Administration of IFN-γ by nebulization to asthmatic patients does not significantly reduce eosinophilic inflammation, possibly because of the difficulty in obtaining a high enough local concentration in the airways[88]. Specific immunotherapy increases IFN-γ production by circulating T cells in patients and has shown clinical benefit in asthma[89]; immunotherapy also increased the number of IFN-γ-expressing cells in nasal biopsies of patients with allergic rhinitis[90]. IFN-γ could be useful in the treatment of patients with severe asthma who have reduced responsiveness to corticosteroids[91].

IL-12 and IL-18 have a synergistic effect on inducing IFN-γ release and inhibiting IL-4-dependent IgE production and AHR[92]; however, there are no reported clinical studies of IL-18 in asthma. IL-12 regulates T_H1 cell development and determines the balance between T_H1 and T_H2 cells, partly through the release of IFN-γ from T_H1 cells to suppress T_H2 cells[93]. In patients with mild asthma, weekly infusions of human recombinant IL-12 in escalating doses over 4 weeks caused a progressive fall in circulating eosinophils, and a reduction

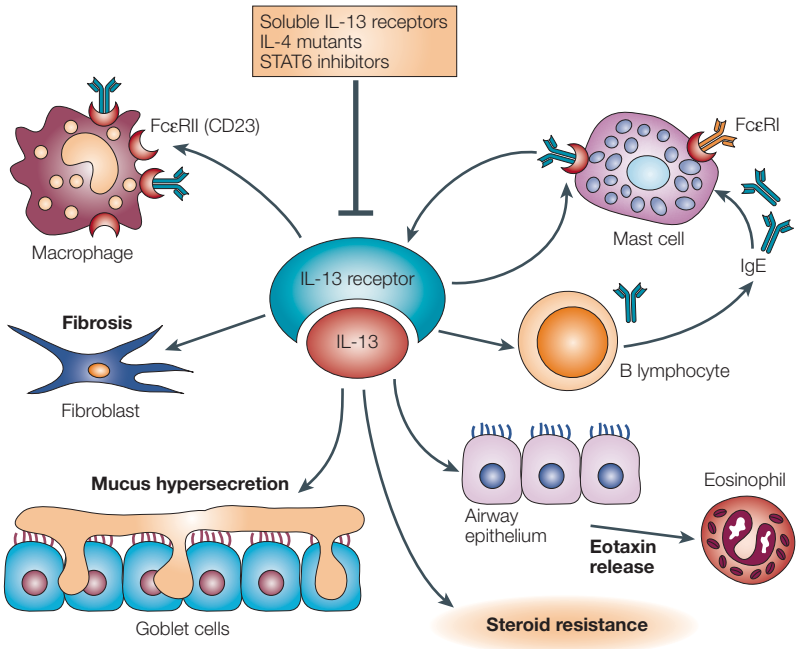

Figure 5 | **Effects of blocking interleukin-13 in asthma.** Interleukin (IL)-13 has several effects relevant to allergic inflammation in asthma, including production of immunoglobulin E (IgE) from B lymphocytes, increased expression for the low-affinity receptor for IgE (FCεRII, CD23) on several inflammatory cells, increased mucus secretion and fibrosis and eotaxin release from airway epithelium. In addition, IL-13 induces steroid resistance (probably by activating p38 mitogen-activated protein kinase). IL-13 can be blocked by a high-affinity soluble receptor (shuIL-13R2), a blocking antibody or an inhibitor of STAT6, which is also activated by IL-4.

in the normal rise in circulating eosinophils after allergen challenge[94]. However, as with anti-IL-5 therapy, there was no reduction in either early or late response to inhaled allergen challenge or any reduction in AHR. Moreover, there was evidence of toxic side effects. Taken together, these findings indicate that recombinant IL-12 is not a suitable treatment for asthma. An IL-12–allergen fusion protein administered to mice resulted in the development of a specific T_H1 response to the allergen, with increased production of an allergen-specific IgG2, rather than the normal T_H2 response with IgE formation[95]. The use of local IL-12 in conjunction with specific allergens might even be curative if applied early in the course of the atopic disease.

Chemokine receptor inhibitors

More than 50 different CHEMOKINES are now recognized to be involved in the recruitment of inflammatory cells via the activation of more than 20 different surface receptors[96]. Chemokine receptors are G-protein-coupled receptors, which makes them amenable to small-molecule inhibitors — an approach that has not yet proved feasible for classical cytokine receptors[97]. Another strategy is to use antibodies, which can produce a long duration of blockade and avoid some of the toxicity issues associated with many small-molecule inhibitors. Some chemokine inhibitors seem to be selective for single chemokines, whereas others are promiscuous and mediate the effects of several related chemokines (FIG. 6).

CHEMOKINE
A small protein mediator that acts as a chemoattractant for inflammatory cells through the activation of chemokine receptors that have the typical structure of G-protein-coupled receptors.

PHOSPHODIESTERASES (PDE). Enzymes that break down cyclic nucleotides in the cell. More than 12 families are now known, but the PDE4 family is prominent in inflammatory cells that are important in asthma.

Several chemokines, including eotaxin, eotaxin-2, eotaxin-3, CCR1 (formerly known as RANTES) and macrophage chemoattractant protein-4 (MCP4) activate chemokine receptor-3 (CCR3) on eosinophils[98]. Accordingly, there is increased expression of eotaxin, eotaxin-2, MCP3, MCP4 and CCR3 in the airways of asthmatic patients and this is correlated with increased AHR[99]. A neutralizing antibody against eotaxin reduces both eosinophil recruitment to the lung after allergen challenge and the associated AHR in mice[100]. Several small-molecule inhibitors of CCR3, including UCB35625, SB-297006 and SB-328437, are effective in inhibiting eosinophil recruitment in allergen models of asthma, and are currently undergoing clinical trials in asthma[101]. There is also evidence for the expression of CCR3 on T_H2 cells and mast cells, and these inhibitors might therefore have a more widespread effect in asthma treatment.

Blocking MCP1-mediated activation of CCR2 on monocytes and T cells using neutralizing antibodies reduced the recruitment of both T cells and eosinophils in a murine model of ovalbumin-induced airway inflammation, with a marked reduction in AHR[100], and blocked the development of AHR in response to allergen in sensitized mice[102]. MCP1 also recruits and activates mast cells, an effect that is mediated via CCR2 (REF. 102). When MCP1 is instilled into the airways in mice, a marked and prolonged reduction of AHR associated with mast-cell degranulation is observed. MCP1 is therefore an attractive target for asthma therapy, and small-molecule inhibitors of CCR2 are now in clinical development.

CCR4 and CCR8 are selectively expressed on T_H2 cells and are activated by the chemokines monocyte-derived chemokine (MDC) and thymus- and activation-dependent chemokine (TARC), both of which are expressed in asthmatic airways[103]. Inhibitors of CCR4 and CCR8 might therefore inhibit the recruitment of T_H2 cells and persistent eosinophilic inflammation in the airways. However, deletion of the *Ccr8* gene in mice has no effect on allergic inflammation, which indicates that this receptor might not be an effective target[104]. The small-molecule compound AMD3100 inhibits allergen-induced inflammation in a murine model of asthma by inhibiting CXCR4, which is selectively expressed on T_H2 cells[105].

Phosphodiesterase-4 inhibitors

PHOSPHODIESTERASES (PDEs) break down cyclic nucleotides that inhibit cell activation (secretion and contraction) and at least ten families of enzymes have now been discovered[106]. Theophylline, long used as an add-on asthma treatment, is a weak, non-selective PDE inhibitor. PDE4 is the predominant member of the PDE family in inflammatory cells[107,108], which indicates that PDE4 inhibitors would be useful as an anti-inflammatory treatment in asthma, particularly as there is some evidence for overexpression of PDE4 in cells of atopic patients (FIG. 7). In animal models of asthma, PDE4 inhibitors reduce eosinophil infiltration and AHR responses to allergen. Several PDE4 inhibitors have been tested in asthma, but with disappointing results[109]. For example, CDP840 had

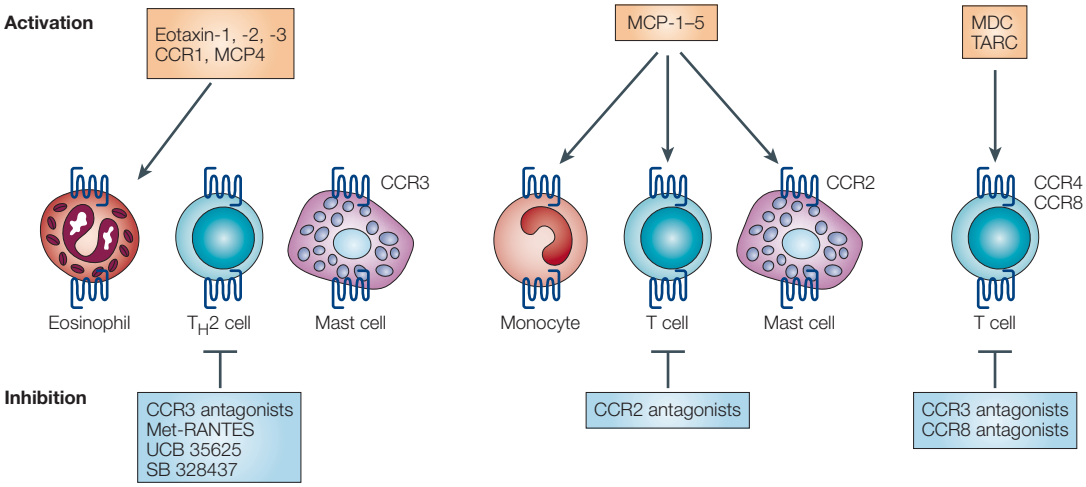

Figure 6 | **Chemokine receptor antagonists in asthma.** Several chemokines are likely to be involved in the pathophysiology of asthma. There are three major chemokine receptor (CCR) targets in asthma: CCR2, CCR3 and CCR4. CCR3 is most advanced in terms of the development of small-molecule inhibitors; in addition, small-molecule inhibitors are now in development for CCR2 and CCR4 (for example, INCB003344 for CCR2). Eotaxins, RANTES (released by activated normal T cells expressed and secreted) and monocyte chemotactic protein-4 (MCP4) all activate CCR3, monocyte chemotactic proteins 1–5 activate CCR2, whereas monocyte-derived chemokine (MDC) and thymus and activation-dependent chemokine (TARC) activate CCR4 and CCR8, which are predominantly expressed on T_H2 cells.

only a marginal inhibitory effect on the late response to allergen and is not being further developed[110], whereas roflumilast seems to be better tolerated and has a long duration of action that makes it suitable for once-daily oral administration[111]. Cilomilast is the PDE4 inhibitor that has been tested most extensively in clinical trials, particularly in chronic obstructive pulmonary disease[112]; however, this drug has a propensity to cause emesis. Indeed, most of the PDE4 inhibitors that have been clinically tested to date have had unacceptable side effects, in particular nausea and vomiting — the same side effects that have limited the use of theophylline. The vomiting is possibly due to inhibition of a particular subtype of PDE4 (cilomilast is known to be selective for this subtype), indicating that the development of subtype-selective inhibitors could be beneficial. PDE4D seems to be of particular importance in nausea and vomiting[113] but is less important in anti-inflammatory effects, and knockout studies indicate that PDE4B is more important than PDE4D in inflammatory cells[114]. PDE4B-selective inhibitors might therefore have a greater therapeutic benefit. Another approach is to administer the PDE4 inhibitor by inhalation: some PDE4 inhibitors have low oral bioavailability but are retained in the lung, and would therefore be suitable for inhaled delivery[115].

Transcription factor inhibitors

Many transcription factors are involved in the expression of inflammatory genes in asthmatic airways and are therefore possible targets for anti-inflammatory drugs.

The pro-inflammatory signalling molecule NF-κB is naturally inhibited by inhibitor of NF-κB (IκB), which is degraded after activation by specific IκB kinases (IKKs). IKK2 is an isoenzyme that is important for activation of NF-κB by inflammatory stimuli[116]. Selective inhibitors of IKK2 or the proteasome (the multifunctional enzyme that degrades IκB), and therefore of NF-κB, are currently in development[117]. However, one concern about long-term NF-κB inhibition is that it could result in immune suppression and impair host defences. As an alternative, there are other pathways of NF-κB activation that might be more important in inflammatory disease and more amenable to long-term modulation[118].

Cyclosporin A, tacrolimus and pimecrolimus inhibit T-lymphocyte function by inhibiting the nuclear factor of activated T-cells (NF-AT) by blocking activation of calcineurin. This results in suppression of IL-2, IL-4, IL-5, IL-13 and granulocyte-macrophage colony stimulating factor (GM-CSF), a cytokine that is important for eosinophil survival; these drugs therefore have therapeutic potential in asthma. However, cyclosporin A is of little value for treating chronic asthma, because the dose is limited by toxicity, in particular nephrotoxicity[119]. Inhaled formulations of cyclosporin and tacrolimus are being tested for efficacy in asthma, but it remains to be determined whether this would provide a favourable therapeutic ratio. Rapamycin (sirolimus) has a similar action to calcineurin inhibitors, but acts more distally and has a better toxicity profile because it is not nephrotoxic; it can, however, induce hyperlipidaemia[120].

GATA-binding protein-3 (GATA3) is important in the differentiation of T_H2 cells and the expression of T_H2 cytokines[121]. Blocking GATA3 with an antisense oligonucleotide or a dominant-negative mutant prevents the differentiation of T_H2 cells and the development of eosinophilic inflammation in mice[121], but the development of a small-molecule inhibitor of GATA3 could be difficult until the specific activation pathways for this transcription factor have been identified. An alternative approach is to activate the opposing transcription factor T-bet, the expression of which is reduced in asthma[122].

CELL-ADHESION MOLECULES
Cell-surface proteins that are involved in the interaction between inflammatory and immune cells and structural cells, such as endothelial or epithelial cells.

Kinase inhibitors

There has been particular interest in the p38 mitogen-activated protein (MAP) kinase pathway, which is involved in expression of several inflammatory proteins that are relevant to asthma[123]. p38 MAP kinase is blocked by a novel class of drugs, the cytokine suppressant anti-inflammatory drugs (CSAIDs), which include SB203580, SB239063 and RWJ67657. These drugs inhibit the synthesis of many inflammatory cytokines, chemokines and inflammatory enzymes. Interestingly, they seem to have a preferential inhibitory effect on synthesis of T_H2 compared with T_H1 cytokines, indicating their potential application in the treatment of atopic diseases[124]. Furthermore, p38 MAP kinase inhibitors decrease eosinophil survival by activating apoptotic pathways[125] and several inhibitors of p38 MAP kinase are now in Phase II development. p38 MAP kinase is also involved in corticosteroid resistance in asthma[126]. Whether this new class of anti-inflammatory drugs will be safe in long-term studies remains to be established; it is likely that such a broad-spectrum anti-inflammatory drug will have some toxicity, but inhalation might be a feasible therapeutic approach.

Jun N-terminal kinases (JNKs) could be involved in activation of the transcription factor AP-1, which is activated in asthmatic airways, and small-molecule inhibitors have now been developed that have anti-inflammatory effects in allergen-exposed sensitized animals[127]. Steroid resistance in asthma is also associated with increased activation of JNKs[128], indicating that JNK inhibitors could be useful in severe asthmatic patients with reduced steroid responsiveness.

Several protein tyrosine kinases have been implicated in allergic inflammation. For example, Syk ($p72^{Syk}$) kinase is pivotal in signalling of the high-affinity IgE receptor (FcεRI) in mast cells. In *syk*-deficient mice, mast-cell degranulation is inhibited, which indicates that this might be an important potential target for the development of mast-cell-stabilizing drugs[129]. Syk is also involved in antigen receptor signalling of B and T lymphocytes and in eosinophil survival in response to IL-5 and GM-CSF[130]. Aerosolized Syk antisense oligodeoxynucleotide inhibits allergen-induced inflammation in a rat model, indicating that this could be a target for asthma drug development[131].

Lyn is a tyrosine kinase that acts upstream of Syk, and its inhibitor kinase, PP1, inhibits inflammation and mast-cell activation[132]. Lyn is also involved in eosinophil activation and IL-5 signalling[133,134], and a Lyn-blocking peptide inhibits eosinophilic inflammation in a murine model of asthma[134]. However, Lyn and Syk are widely distributed in the immune system, so there are consequently concerns about the long-term safety of selective inhibitors of these kinases.

Cell-adhesion blockers

Infiltration of inflammatory cells into tissues is dependent on the adhesion of blood-borne inflammatory cells to endothelial cells before migration to the inflammatory site[135]. This requires specific glycoprotein adhesion molecules, such as integrins and selectins, on both leukocytes and on endothelial cells, which are upregulated and show increased binding affinity in response to various inflammatory stimuli. Monoclonal antibodies that inhibit adhesion molecules can therefore prevent infiltration by inflammatory cells. A monoclonal antibody against intercellular adhesion molecule-1 (ICAM1) on endothelial cells prevents the infiltration of eosinophils into airways and the increase in bronchial reactivity after allergen exposure in sensitized primates[136], although this has not been found in other species[137].

The interaction between the α4 integrin very late antigen-4 (VLA4) and vascular cell-adhesion molecule-1 (VCAM1) is important for eosinophil inflammation[138]. Small-molecule peptide inhibitors of VLA4 have been developed that inhibit allergen-induced responses in sensitized sheep[139] and are now in clinical trials for asthma. Moreover, natalizumab (Antegren; Elan), a monoclonal antibody against α4 integrin, a component of VLA4, has recently been shown to be effective in Crohn's disease, indicating its anti-inflammatory efficacy in humans[140]. Inhibitors of selectins based on the structure of sialyl-Lewis^x (particularly L-selectin, which is expressed on granulocytes and T lymphocytes) inhibit the influx of inflammatory cells in response to inhaled allergen in sensitized sheep[141] and inhibit adhesion of human eosinophils *in vitro*[142]. However, there could be potential dangers associated with inhibiting immune responses by preventing T-cell trafficking, because this could lead to an increased risk of infection and neoplasia.

Anti-allergy drugs

Anti-allergy drugs have the potential to more selectively target the atopic disease process. There are several approaches to inhibiting allergen-induced responses (FIG. 8).

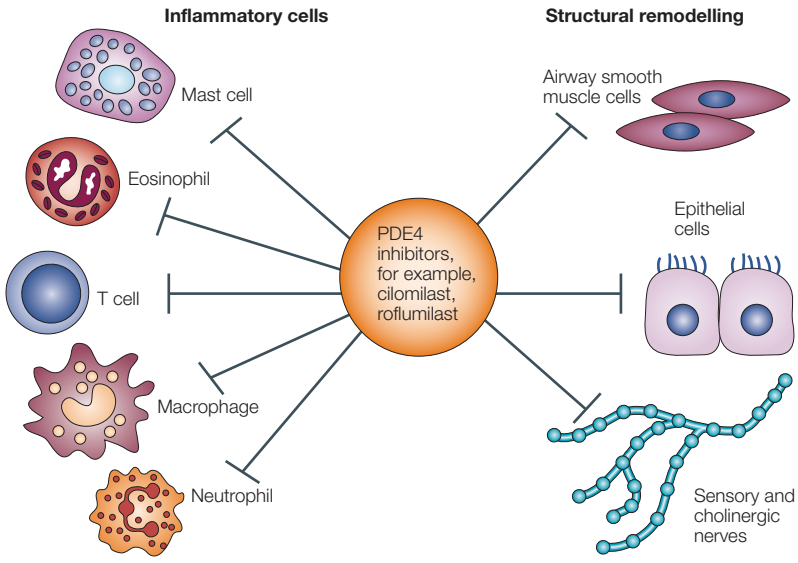

Figure 7 | **Phosphodiesterase-4 inhibitors have a broad spectrum of anti-inflammatory effects in asthma.** Phosphodiesterase-4 (PDE4) inhibitors inhibit the recruitment and activation of key inflammatory cells, including mast cells, eosinophils, T lymphocytes, macrophages and neutrophils, as well as the hyperplasia and hypertrophy of structural cells, including airway smooth-muscle cells, epithelial cells and sensory and cholinergic nerves.

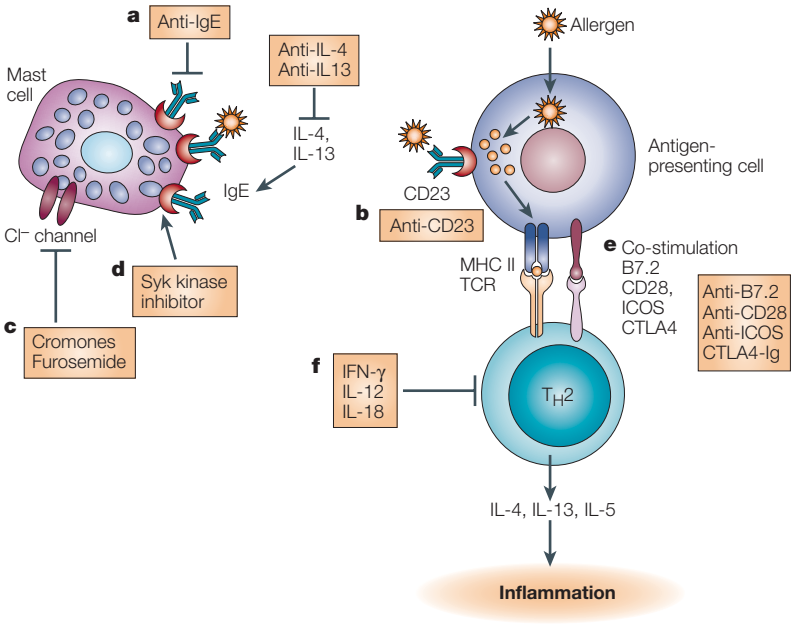

Figure 8 | **Strategies to inhibit the allergic response underlying asthma.** Immunoglobulin E (IgE) can be inhibited by the antibody omalizumab (**a**) and low-affinity IgE receptors by anti-CD23 (**b**). Mast cells can also be blocked by cromones and furosemide (**c**), probably acting on a chloride channel and by inhibitors of Syk kinase, which inhibit the signal-transduction pathways activated by IgE receptors (**d**). Antigen presentation can be blocked by inhibitors of co-stimulatory molecules (**e**), including B7.2, CD28, inducible co-stimulatory molecule (ICOS) and cytotoxic T-lymphocyte antigen-4 (CTLA4). T_H2 cells can also be directly inhibited by interferon-γ (IFN-γ), interleukin (IL)-12 and IL-18 (**f**).

Cromones. Sodium cromoglycate (cromolyn sodium) and nedocromil sodium are the most specific anti-allergy drugs so far discovered, but their effectiveness is considerably less than low doses of inhaled corticosteroids, probably because of their short duration of action. Cromones have a specific action on allergic inflammation, yet their molecular mechanism of action remains obscure. Although it was believed that their primary mode of action involves inhibiting mast-cell mediator release, cromones also inhibit other inflammatory cells and sensory nerves, and can act on and possibly inhibit certain types of chloride channels that are expressed in mast cells and sensory nerves[143,144]. The identification of the molecular mechanism of action could aid the development of more potent and long-lasting cromone-like drugs in the future. Both cromoglycate and nedocromil must be given topically, and all attempts to develop orally active drugs of this type have been unsuccessful, which perhaps indicates that topical administration is crucial to their efficacy.

Furosemide. The diuretic furosemide (frusemide) shares many of the actions of cromones; for example, both classes of drug inhibit indirect bronchoconstrictor challenges but not direct bronchoconstriction (histamine, methacholine) when given by inhalation[145]. The mechanism of action of furosemide is thought to involve inhibition of the same chloride channel that is inhibited by cromones. Furosemide itself does not seem to be very effective when given regularly by metered-dose inhaler in asthma[146], but it is possible that more potent and long-lasting chloride-channel blockers might be developed in the future.

Co-stimulation inhibitors. CO-STIMULATORY MOLECULES might be crucial in augmenting the interaction between antigen-presenting cells and $CD4^+$ cells[147]. For example, the interaction between B7 and CD28 might determine which type of T-cell response develops, and there is some evidence that B7.2 (CD86) promotes a T_H2 response. Antibodies against B7.2 inhibit the development of specific IgE response, pulmonary eosinophilia and AHR in mice, whereas antibodies to B7.1 (CD80) are ineffective[148].

Cytotoxic T-lymphocyte-associated antigen-4 (CTLA4), a molecule expressed on activated T cells, is another co-stimulator of T-cells[149]. Correspondingly, the soluble fusion protein CTLA4-Ig, which inhibits CTLA4 function, blocks the development of AHR in a murine model of asthma[150], although it seems to be less effective when the allergic inflammation is severe[151]. Anti-CD28, anti-B7.2 and CTLA4-Ig also block the proliferative response of T cells to allergen[152], indicating that these are potential targets for novel therapies that should be effective in all atopic diseases.

Another co-stimulatory molecule — inducible co-stimulatory molecule (ICOS) — is related to CD28 and binds to the B7-like molecule B7RP-1. ICOS seems to be important in polarizing the immune response, and an antibody to ICOS blocks the development of T_H2 cells, whereas CD28 plays a role in priming T cells[153]. This means that blocking ICOS could inhibit T_H2 cell development, thereby inhibiting allergic inflammation.

Anti-IgE. The release of mediators from mast cells in asthma is IgE-dependent, and blocking the activation of IgE using antibodies that do not result in cell activation is therefore an attractive approach to treat asthma. A humanized monoclonal antibody directed to the high-affinity IgE-receptor (FcεRI)-binding domain of human IgE (omalizumab) has beneficial effects in the treatment of patients with asthma when given by subcutaneous injection every 2–4 weeks, particularly for those with severe steroid-dependent disease[154]. Omalizumab is now approved for asthma therapy in some countries, but its high cost means that it is only likely to be used in patients with very severe disease that is not controlled by low doses of oral corticosteroids. However, the success of omalizumab indicates that small-molecule inhibitors of IgE-activated signal-transduction pathways might be beneficial.

Anti-CD23. CD23 is a low-affinity IgE receptor (FcεRII) that mediates the effects of IgE on inflammatory cells other than mast cells, including B lymphocytes that produce IgE. An antibody to CD23, IDEC-152, reduces IgE in asthmatic patients and is in clinical trials for the evaluation of efficacy[155].

CO-STIMULATORY MOLECULES Surface proteins on antigen-presenting cells and T lymphocytes that enhance the interaction between the T-cell receptor and the major histocompatibility complex.

Table 2 | **New therapeutic strategies for asthma**

Class	Example
New glucocorticoids	Ciclesonide and dissociated steroids
Immunomodulators	Inhaled cyclosporin, tacrolimus, rapamycin and mycophenolate mofetil (CellCept; Roche)
Phosphodiesterase-4 inhibitors	Cilomilast and roflumilast
p38 MAP kinase inhibitors	CSAIDs, for example, SB203580, SB239063 and RWJ67657
Nuclear factor-κB pathway inhibition	Inhibitor of nuclear factor-κB kinase-2 (IKK-2) inhibitors
Adhesion molecule blockers	Inhibitors of very late antigen-4 and selectin
Cytokine inhibitors	Anti-interleukin (IL)-4, anti-IL-5, anti-IL-13, anti-IL-9 and anti-tumour-necrosis factor antibodies
Anti-inflammatory cytokines	Interferon-γ, IL-10, IL-12 and IL-18
Chemokine receptor (CCR) antagonists	CCR3, CCR2 and CCR4 antagonists
Anti-allergic drugs	Anti-immunoglobulin E, anti-CD23 antibodies and co-stimulatory molecule inhibitors
Peptides for immunotherapy	House dust-mite allergen
Vaccines	BCG inoculation

MAP, mitogen-activated protein.

Vaccines, immunotherapy and immunostimulation

Specific immunotherapy. Immunotherapy — the subcutaneous injection of small amounts of purified allergen — has been used for many years in the treatment of allergy, but it is not very effective in asthma and has a risk of serious side effects. The molecular mechanism of desensitization is unknown, but might be related to stimulation of IL-10 and release of transforming growth factor-β from a subset of regulatory T cells[84]. The cloning of several common allergen genes has made it possible to prepare recombinant allergens for injection, although this purity might detract from their allergenicity, because most natural allergens contain several proteins. In rats, an intramuscular injection of plasmid DNA expressing house dust-mite allergen prevents the development of IgE responses to inhaled allergen[156]. This indicates that allergen gene immunization with a DNA vaccine might be a therapeutic strategy for asthma in the future.

T-cell peptides. T-cell-derived peptides from cat allergen (*fel* d1) seem to be effective in blocking allergen responses to cat dander, but can induce an isolated late response to allergen by direct T-cell activation followed by prolonged hyporesponsiveness[157]. *Fel* d1 peptides inhibit the cutaneous response to cat allergens, but whether this will be a useful strategy in asthma is not yet certain. One problem of this approach is that there are differences between individuals in the ability of their immune system to recognize T-cell peptide epitopes, so this approach might not be effective in all patients; in addition, many patients are sensitized to more than one allergen.

Vaccination. A relative lack of infections might be a factor that influences the development of atopy in genetically predisposed individuals; this possibility has led to the idea of using vaccination to induce protective T_H1 responses that in turn prevent sensitization and therefore the development of atopic diseases. BCG inoculation in mice 14 days before allergen sensitization reduced the formation of specific IgE in response to allergen, as well as the eosinophilic response and AHR responses to allergen, with an increase in the production of IFN-γ[158]. This has prompted several clinical trials of BCG to prevent the development of atopy. In one study, BCG vaccination was shown to improve asthma control and reduce markers of T_H2 activation[159].

CpG oligonucleotides. Immunostimulatory DNA sequences, such as unmethylated cytosine-guanosine dinucleotide-containing oligonucleotides (CpG ODNs), are also potent inducers of T_H1 cytokines because they stimulate IL-12 release[160]. The administration of CpG ODN to mice increases the ratio of T_H1 to T_H2 cells, decreases the formation of specific IgE and reduces the eosinophilic response to allergen, an effect which lasts for more than six weeks[161]. CpG ODN treatment is also able to reverse established allergen-driven eosinophilic inflammation in mice[162] and to reverse AHR in mice sensitized to ragweed pollen antigen[163]. These promising animal studies buttress the idea that CpG ODN and DNA vaccines might prevent or cure atopic diseases in the future, and clinical trials of these compounds are currently underway[164].

Although approaches aimed at tipping the balance of the immune system towards a T_H1 response are promising in terms of disease modification, there are concerns that a therapeutic shift might increase the chance that individuals develop T_H1-mediated diseases, such as autoimmune diseases, multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis and diabetes. These concerns particularly apply to infants.

Antisense and gene therapy

Atopic diseases are polygenic, and so it is unlikely that gene or antisense therapy will be of value in the long-term. However, an understanding of the genes involved in atopic diseases and in disease severity might help in the identification of new molecular targets[165] and could also aid the prediction of responses to different forms of therapy[166]. Several novel genes have recently been linked to asthma[167] and potentially provide the basis for the development of antisense therapeutics; however, there are considerable challenges with the intracellular delivery of these molecules.

Antisense oligonucleotides. An inhaled antisense oligonucleotide directed against the adenosine A_1 receptor reduced AHR in a rabbit model of asthma, thereby demonstrating the potential of this delivery route[168]. Respirable antisense oligonucleotides (RASONS) are a novel approach to asthma therapy, and clinical trials with the A_1 receptor oligonucleotide EPI-2010 (EpiGenesis) have shown that this therapy is well tolerated[169]. Decoy double-stranded oligonucleotides containing the DNA-binding motif of transcription factors look promising as blockers of specific transcription factors, such as NF-κB and STATs[170].

RNA interference. The relatively new technology of RNA interference (RNAi) has proved invaluable in determining the function of specific genes in human cells, but RNAi also has potential therapeutic applications[171]. This technique seems to be more effective than antisense oligonucleotides in switching off genes, although there are problems of intracellular delivery associated with the small interfering RNA (siRNA) sequences used in RNAi approaches. Recent studies indicate that the nasal application of siRNA sequences might inhibit gene expression in the lungs without the need for viral vectors[172].

Conclusions

Many different therapeutic approaches to the treatment of asthma are possible (TABLE 2), yet there have been few new drugs during the past 30 years that have reached the clinic. Inhaled corticosteroids are very effective as a chronic treatment for asthma, and are capable of suppressing the underlying inflammatory process. It is likely that combination inhalers that include a corticosteroid and long-acting β_2 agonist will remain the principal approach to asthma therapy for at least the next 10 years, particularly as once-daily combinations become available. An advance in therapy would be the development of more specific anti-asthma drugs that lack side effects. If such treatments could be taken orally, then they might also be applicable to the treatment of atopic diseases, such as rhinitis and eczema, which often coincide with asthma.

It is difficult to imagine that any of the therapies now in development will be more effective than combination inhalers. Blocking a single mediator or cytokine is unlikely to be as effective, as such treatments are too specific. There is more hope for anti-inflammatory therapies, such as PDE4, p38 MAP kinase and IKK2 inhibitors, although these drugs are likely to have dose-limiting side effects, which might require inhaled administration. Drugs that affect the underlying allergic response (and therefore also treat allergic rhinitis and dermatitis) are of interest, and have been pioneered by anti-IgE antibody. Inhibitors of co-stimulatory molecules are currently being explored, together with vaccination strategies to reverse the immunological abnormalities underlying the allergic response. The possibility of developing a 'cure' for asthma is remote, but strategies to inhibit the development of sensitization in early childhood offer such a prospect in the future.

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Competing interests statement
The author declares competing financial interests: see Web version for details.

Online links

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