Abstract
Multiple cytokines play a critical role in orchestrating and perpetuating inflammation in asthma and several specific cytokine and chemokine inhibitors are now in development as future therapy. Anti-interleukin (IL)-5 antibodies markedly reduce peripheral blood and airway eosinophils, but do not appear to be effective in symptomatic asthma. Inhibition of IL-4, despite promising early results in asthma, has been discontinued and blocking IL-13 may be more effective. Inhibitory cytokines, such as IL-10, interferons and IL-12 are less promising, because systemic delivery produces side-effects. Inhibition of tumor necrosis factor (TNF)-α may be useful in severe asthma. Many chemokines are involved in the inflammatory response of asthma and several small molecule inhibitors of chemokine receptors are in development. The CCR3 antagonists (which block eosinophil chemotaxis) are in clinical development for asthma. Because so many cytokines are involved in asthma, drugs that inhibit the synthesis of multiple cytokines may prove to be more useful; several such classes of drug are now in clinical development and any risk of side-effects with these non-specific inhibitors may be reduced by the inhaled route.

Key words: chemokines, interleukin-4, interleukin-5, interleukin-10, interleukin-12, interleukin-13, tumor necrosis factor-α.

Introduction
Cytokines play a critical role in the orchestration of chronic inflammation in all diseases, including asthma. Multiple cytokines and chemokines have been implicated in the pathophysiology of asthma. There is now an intensive search for more specific therapies in asthma. Inhibitors of cytokines and chemokines figure prominently in these novel therapeutic approaches (Table 1).

Strategies for inhibiting cytokines
There are several possible approaches to inhibiting specific cytokines. These range from drugs that inhibit cytokine synthesis (glucocorticoids, cyclosporine A, tacrolimus, rapamycin, mycophenolate, T helper 2 (Th2)-selective inhibitors), humanized blocking antibodies to cytokines or their receptors, soluble receptors to mop up secreted cytokines, small molecule receptor antagonists or drugs that block the signal transduction pathways activated by cytokine receptors. In contrast, there are cytokines that themselves suppress the allergic inflammatory process and these may have therapeutic potential in asthma.

Inhibition of Th2 cytokines
The Th2 lymphocytes play a key role in orchestrating the eosinophilic inflammatory response in asthma, suggesting that blocking the release or effects of these cytokines may have therapeutic potential. This has been strongly supported by studies in experimental animals, including mice with deletion of the specific Th2 cytokine genes.

Anti-interleukin-5
Interleukin (IL)-5 plays an essential role in orchestrating the eosinophilic inflammation of asthma. In IL-5 gene knock-out mice, the eosinophilic response to allergen and the subsequent airway hyperresponsiveness (AHR) are markedly suppressed and yet animals have a normal survival, validating the strategy to inhibit IL-5. This has also been achieved using blocking antibodies to IL-5.
Blocking antibodies to IL-5 inhibit eosinophilic inflammation and AHR in animal models of asthma, including primates. This blocking effect may last for up to 3 months after a single intravenous injection of antibody in primates, making treatment of chronic asthma with such a therapy a feasible proposition. Humanized monoclonal antibodies to IL-5 have been developed and a single intravenous infusion of one of these antibodies (mepolizumab) markedly reduces blood eosinophils for several weeks and prevents eosinophil recruitment into the airways after allergen challenge in patients with mild asthma (Fig. 1). However, this treatment has no significant effect on the early or late response to allergen challenge or on baseline AHR, suggesting that eosinophils may not be of critical importance for these responses in humans (Fig. 2). A clinical study in patients with moderate to severe asthma who had not been controlled on inhaled corticosteroid therapy confirmed a

Table 1  Cytokine modulators for asthma

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IL, interleukin; TNF-α, tumor necrosis factor-α; IFN, interferon; NF-κB, nuclear factor-κB; IKK, inhibitor of NF-κB kinase; MAPK, mitogen-activated protein kinase.

Fig. 1  Effect of a humanized monoclonal antibody against interleukin-5 (mepolizumab) on circulating eosinophils in patients with mild asthma, demonstrating a profound and very prolonged inhibitory effect. (▲), placebo (n = 8); (■), 2.5 mg/kg mepolizumab (n = 8); (●), 10 mg/kg mepolizumab (n = 8). B/L, baseline; D, day; Wk, week. Adapted from Leckie et al.⁶
profound reduction in circulating eosinophils, but no significant improvement in either asthma symptoms or lung function.\textsuperscript{7} In both these studies, it would be expected that high doses of corticosteroids would improve these functional parameters.\textsuperscript{6,7} These surprising results question the critical role of eosinophils in asthma and indicate that other strategies aimed at inhibiting eosinophilic inflammation may not be effective. More recently, a biopsy study has demonstrated that anti-IL-5 antibody, while profoundly reducing eosinophils in the circulation (by over 95%), is less effective at reducing eosinophils in bronchial biopsies (by approximately 50%), which may explain why this treatment is not clinically effective.\textsuperscript{8} Nevertheless, this suggests that blocking IL-5 is not likely to be a useful approach to asthma therapy.

Somewhat similar findings have been reported previously in some studies in mice, where anti-IL-5 antibodies reduced eosinophilic responses to allergen, but not AHR, whereas AHR was reduced by anti-CD4 antibody, which depletes Th cells\textsuperscript{9} and suggests that T cell-derived cytokines other than IL-5 must be playing a more important role in AHR.

Non-peptidic IL-5 receptor antagonists would be an alternative strategy and there is a search for such compounds using molecular modeling of the IL-5 receptor α-chain and through large-scale throughput screening. One such molecule, YM-90709, appears to be a relatively selective inhibitor of IL-5-receptors.\textsuperscript{10} However, the lack of clinical benefit of anti-IL-5 antibodies has made this a less attractive approach. It is possible that eosinophils are associated with more chronic aspects of asthma, such as airway remodeling, and, in mice, a blocking anti-IL-5 antibody prevents the increased collagen deposition in airways associated with repeated allergen exposure.

**Anti-IL-4**

Interleukin-4 is critical for the synthesis of IgE by B lymphocytes and is also involved in eosinophil recruitment to the airways.\textsuperscript{11} A unique function of IL-4 is to promote differentiation of Th2 cells and, therefore, it acts at a proximal and critical site in the allergic response, making IL-4 an attractive target for inhibition.

Interleukin-4 blocking antibodies inhibit allergen-induced AHR, goblet cell metaplasia and pulmonary eosinophilia in a murine model.\textsuperscript{11} Therefore, inhibition of IL-4 may be effective in inhibiting allergic diseases and soluble humanized IL-4 receptors (sIL-4R) have been tested in clinical trials. A single nebulized dose of sIL-4R prevents the fall in lung function induced by withdrawal of
inhaled corticosteroids in patients with moderately severe asthma.\textsuperscript{12} Subsequent studies have demonstrated that weekly nebulization of sIL-4R improves asthma control over a 12 week period.\textsuperscript{13} However, subsequent studies in patients with milder asthma proved disappointing and this treatment has now been withdrawn. Another approach is blockade of IL-4 receptors with a mutated form of IL-4 (BAY 36-1677), which binds to and blocks IL-4Rα and IL-13Rα1, thus blocking both IL-4 and IL-13.\textsuperscript{14} This treatment has also been withdrawn.

Interleukin-4 and the closely related cytokine IL-13 signal through a shared surface receptor, namely IL-4Rα, which activates a specific transcription factor, signal transducers and activators of transcription (STAT)-6.\textsuperscript{15} Deletion of the STAT-6 gene has a similar effect to IL-4 gene knock-out. This has led to a search for inhibitors of STAT-6 and, although peptide inhibitors that interfere with the interaction between STAT-6 and Janus kinase (JAK) linked to IL-4Rα have been discovered, it will be difficult to deliver these intracellularly. An endogenous inhibitor of STAT, suppressor of cytokine signaling (SOCS-1), is a potent inhibitor of IL-4 signaling pathways and offers a new therapeutic target.\textsuperscript{15}

**Anti-IL-13**

There is increasing evidence that IL-13 in mice mimics many of the features of asthma, including AHR, mucus hypersecretion and airway fibrosis, independently of eosinophilic inflammation.\textsuperscript{16} It potently induces the secretion of eotaxin from airway epithelial cells and transforms airway epithelium into a secretory phenotype. Knocking out the IL-13, but not the IL-4, gene in mice prevents the development of AHR after allergen, despite a vigorous eosinophilic response, and the increase in AHR induced by IL-13 is only seen when the expression of STAT-6 is lost in airway epithelial cells.\textsuperscript{16} Interleukin-13 signals through the IL-4Rα, but may also activate different intracellular pathways via activation of IL-13Rα1,\textsuperscript{15} so that it may be an important 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, thus 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.\textsuperscript{17} In the murine model, IL-13Rα2 is more effective than IL-4-blocking antibodies,\textsuperscript{16} highlighting the potential importance of IL-13 as a mediator of allergic inflammation. Blocking IL-13 may be more important in established asthma, where concentrations of IL-13 are much higher than those of IL-4. Humanized IL-13Rα2 is now in clinical development as a therapeutic approach for asthma.

**Anti-IL-9**

Interleukin-9 is a Th2 cytokine that may enhance Th2-driven inflammation and amplify mast cell mediator release and IgE production.\textsuperscript{18} Interleukin-9 may also enhance mucus hypersecretion. Interleukin-9 and its receptors show an increased expression in asthmatic airways.\textsuperscript{19} A blocking antibody to IL-9 inhibits airway inflammation and AHR in a murine model of asthma.\textsuperscript{20} Strategies to block IL-9, including blocking humanized antibodies, are now in development.\textsuperscript{21}

**Anti-IL-25**

Interleukin-25 is a newly described cytokine that stimulates the release of Th2 cytokines IL4, IL-5 and IL-13, suggesting that it may play a role in allergic inflammation.\textsuperscript{22} It is released from mast cells via an IgE-dependent mechanism and is, therefore, a possible target for inhibition in the treatment of asthma.\textsuperscript{23}

**INHIBITION OF PRO-INFLAMMATORY CYTOKINES**

Pro-inflammatory cytokines, particularly IL-1β and tumor necrosis factor (TNF)-α, may amplify the inflammatory response in asthma and may be linked to disease severity. This suggests that blocking IL-1β or TNF-α may have beneficial effects, particularly in severe airway disease.

**Anti-IL-1**

Interleukin-1 expression is increased in asthmatic airways\textsuperscript{24} and activates many inflammatory genes that are expressed in asthma. There are no small molecule inhibitors of IL-1, but a naturally occurring cytokine, the IL-1 receptor antagonist (IL-1ra), binds to IL-1 receptors to block the effects of IL-1. In experimental animals IL-1ra reduces AHR induced by allergen. However, human recombinant IL-1ra does not appear to be effective in the treatment of asthma.\textsuperscript{25}

**Anti-TNF**

Tumor necrosis factor-α is expressed in asthmatic airways and may play a key role in amplifying asthmatic inflammation, through the activation of nuclear factor
(NF)-κB, activating protein (AP)-1 and other transcription factors. In rheumatoid arthritis and inflammatory bowel disease, blocking humanized monoclonal antibodies to TNF-α (infliximab) and soluble TNF receptors (etanercept) have produced remarkable clinical responses, even in patients who are relatively unresponsive to steroids. Such TNF inhibitors are a logical approach to asthma therapy, particularly in patients with severe disease, and clinical trials are now underway.

Because of the problems associated with antibody based therapies that have to be given by injection, there is a search for small molecule inhibitors of TNF. Tumor necrosis factor-α-converting enzyme (TACE) is a matrix metalloproteinase-related enzyme critical for the release of TNF from the cell surface. Small molecule TACE inhibitors are in development as oral TNF inhibitors.27

**Anti-inflammatory cytokines**

Some cytokines have anti-inflammatory effects in inflammation and, therefore, have therapeutic potential.3 Wherein it may not be feasible or cost-effective to administer these proteins as long-term therapy, it may be possible to develop drugs in the future that increase the release of these endogenous cytokines or activate their receptors and specific signal transduction pathways.

**Interleukin-10**

Interleukin-10 is a potent anti-inflammatory cytokine that inhibits the synthesis of many inflammatory proteins, including cytokines (TNF-α, granulocyte–macrophage colony stimulating factor (GM-CSF), IL-5, chemokines) and inflammatory enzymes (inducible nitric oxide synthase) that are overexpressed in asthma.28 Indeed, there may be a defect in IL-10 transcription and secretion from macrophages in asthma, suggesting that IL-10 may be defective in atopic diseases.29,30 In sensitized animals, IL-10 is effective in suppressing the inflammatory response to allergens31 and CD4+ cells engineered to secrete IL-10 suppress airway inflammation in a murine model of asthma.32 Specific allergen immunotherapy results in increased production of IL-10 by Th cells and this may contribute to the beneficial effects of immunotherapy.33

Recombinant human IL-10 has proved to be effective in controlling inflammatory bowel disease and psoriasis, where similar cytokines are expressed, and may be given as a weekly injection.34 Although IL-10 is reasonably well tolerated, there are hematological side-effects. In the future, drugs that activate the unique signal transduction pathways activated by the IL-10 receptor or drugs that increase endogenous production of IL-10 may be developed. In mice, drugs that elevate cAMP increase IL-10 production, but this does not appear to be the case in human cells.35

**Interferons**

Interferon (IFN)-γ inhibits Th2 cells and should, therefore, reduce atopic inflammation. In sensitized animals, nebulized IFN-γ inhibits eosinophilic inflammation induced by allergen exposure and adenovirus-mediated gene transfer of IFN-γ inhibits allergic inflammation in mice.36 However, administration of IFN-γ by nebulization to asthmatic patients did not significantly reduce eosinophilic inflammation, possibly due to the difficulty in obtaining a high enough concentration locally in the airways.37 Interestingly, allergen immunotherapy increases IFN-γ production by circulating T cells in patients with clinical benefit38 and increases the numbers of IFN-γ-expressing cells in nasal biopsies of patients with allergic rhinitis.39 A preliminary report suggests that IFN-α may be useful in the treatment of patients with severe asthma who have reduced responsiveness to corticosteroids.40

**Interleukin-12**

Interleukin-12 is the endogenous regulator of Th1 cell development and determines the balance between Th1 and Th2 cells.41 Interleukin-12 administration to rats inhibits allergen-induced inflammation and inhibits sensitization to allergens. Interleukin-12 releases IFN-γ, but has additional effects on T cell differentiation. Interleukin-12 levels released from whole blood cells are lower in asthmatic patients, indicating a possible reduction in IL-12 secretion.42 Recombinant human IL-12 has been administered to humans and has several toxic effects that are diminished by slow escalation of the dose.43 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 in the normal rise in circulating eosinophils after allergen challenge44 (Fig. 3). There was a concomitant reduction in eosinophils in induced sputum. However, there was no reduction in either the early or late response to inhaled allergen challenge or any reduction in AHR (as with anti-IL-5
therapy). Furthermore, most patients suffered from malaise and one of the 12 subjects had an episode of cardiac arrhythmia. This suggests that IL-12 is not a suitable treatment for asthma. In mice, administration of an IL-12–allergen fusion protein results in the development of a specific Th1 response to the allergen, with increased production of an allergen-specific IgG2, rather than the normal Th2 response with IgE formation. This indicates the possibility of using local IL-12 together with specific allergens to provide a more specific immunotherapy, which may even be curative if applied early in the course of the atopic disease.

Interleukin-18 and IL-23

Interleukin-18 was originally described as IFN-γ-releasing factor, but has a different mechanism of action to IL-12. Interleukin-12 and IL-18 appear to have a synergistic effect on inducing IFN-γ release and for inhibiting IL-4-dependent IgE production and AHR, but no clinical studies have been reported so far.

Interleukin-23 is structurally related to IL-12 and shares some of its biological effects, so should have a protective function in asthma. Its clinical potential has not yet been explored.

Chemokine Inhibitors

Many chemokines are involved in the recruitment of inflammatory cells in asthma. Over 50 different chemokines are now recognized and they activate up to 20 different surface receptors. Chemokine receptors belong to the seven transmembrane receptor superfamily of G-protein-coupled receptors and this makes it possible to find small molecule inhibitors and this makes it possible to find small molecule inhibitors, which has not yet been possible for classic cytokine receptors. Some chemokines appear to be selective for single chemokines, whereas others are promiscuous and mediate the effects of several related chemokines (Fig. 4). Chemokines appear to act in sequence in determining the final inflammatory response and so inhibitors may be more or less effective depending on the kinetics of the response.

CCR3 inhibitors

Several chemokines, including eotaxin, eotaxin-2, eotaxin-3, RANTES and macrophage chemotactic protein (MCP)-4, activate a common receptor on eosinophils designated CCR3. A neutralizing antibody against eotaxin reduces eosinophil recruitment into the lung after allergen and the associated AHR in mice. There is increased expression of eotaxin, eotaxin-2, MCP-3, MCP-4 and CCR3 in the airways of asthmatic patients and this is correlated with increased AHR. 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 drugs in this class are currently undergoing clinical trials in asthma. Although it was thought that CCR3 were restricted to eosinophils, there is some evidence for their expression on Th2 cells and mast cells, so that these inhibitors may have a more widespread
effect than on eosinophils alone, making them potentially more valuable in asthma treatment.

RANTES, which shows increased expression in asthmatic airways, also activates CCR3, but also has effects on CCR1 and CCR5, which may play a role in T cell recruitment. Modification of the N-terminal of RANTES (met-RANTES) has a blocking effect on RANTES by inhibiting these receptors.57

**CCR2 inhibitors**

Macrophage chemoattractant protein-1 activates CCR2 on monocytes and T lymphocytes. Blocking MCP-1 with neutralizing antibodies reduces recruitment of both T cells and eosinophils in a murine model of ovalbumin-induced airway inflammation, with a marked reduction in AHR.53 Macrophage chemoattractant protein-1 also recruits and activates mast cells, an effect that is mediated via CCR2. Macrophage chemoattractant protein-1 instilled into the airways induces marked and prolonged AHR in mice, associated with mast cell degranulation. A neutralizing antibody to MCP-1 blocks the development of AHR in response to allergen.58 Macrophage chemoattractant protein-1 levels are increased in bronchoalveolar lavage fluid of patients with asthma.59 This has led to a search for small molecule inhibitors of CCR2.

**Other CCR inhibitors**

CCR4 and CCR8 are selectively expressed on Th2 cells and are activated by the chemokines monocyte-derived chemokine (MDC) and thymus and activation-dependent chemokine (TARC).60 Therefore, inhibitors of CCR4 and CCR8 may inhibit the recruitment of Th2 cells and, thus, persistent eosinophilic inflammation in the airways. CCR8 gene deletion does not have any effects on allergic inflammation in mice, suggesting that this receptor may not be an effective target.61 In addition, CXC receptor (CXCR) 4 is selectively expressed on Th2 cells and a small molecule inhibitor (AMD3100) inhibits allergen-induced inflammation in a murine model of asthma.62
CCR7 plays a role in the migration of dendritic cells to regional lymph nodes and, therefore, blocking this receptor may suppress antigen presentation.\textsuperscript{63}

**CXCR inhibitors**

CXC receptors mediate the effects of CXC chemokines, which act predominantly on neutrophils and monocytes. Neutrophils are not a prominent feature of inflammation in patients with chronic asthma and inflammation is dominated by eosinophils. However, there is evidence for increased neutrophils in biopsies and induced sputum of patients with severe asthma who are treated with high doses of inhaled or oral corticosteroids, and the levels of IL-8 are increased.\textsuperscript{64,65} It is not certain whether this neutrophilic inflammation contributes to pathophysiology, but it is possible that CXCR2 inhibitors may have a therapeutic role in severe asthma.

**Other approaches to cytokine inhibition**

Although there have been several attempts to block specific cytokines, this may not be adequate to block chronic inflammation in asthma, because so many cytokines are involved and there is considerable redundancy of effects. This has suggested that the development of drugs that have a more general effect on cytokine synthesis may be more successful. However, these drugs also affect other inflammatory processes, so their beneficial effects cannot necessarily be ascribed to inhibition of cytokine synthesis alone.

**Corticosteroids**

Corticosteroids are, by far, the most effective treatments for asthma and part of their efficacy is due to inhibition of inflammatory cytokine expression. This is mediated via an effect on glucocorticoid receptors to reverse the acetylation of core histones, which is linked to increased expression of inflammatory genes, such as those encoding cytokines and chemokines.\textsuperscript{66}

**Immunomodulatory drugs**

Cyclosporine A, tacrolimus and rapamycin inhibit the transcription factor nuclear factor of activated T cells (NF-AT), which regulates the secretion of IL-2, IL-4, IL-5, IL-13 and GM-CSF by T lymphocytes.\textsuperscript{67} Although it has some reported beneficial steroid-sparing effects in asthma, the toxicity of cyclosporine A limits its usefulness, at least when given orally. More selective Th2 selective drugs may be safer for the treatment of asthma in the future. An inhibitor of Th2 cytokines, namely suplatast tosilate,\textsuperscript{68} provides clinical benefit in asthma.\textsuperscript{69}

**Phosphodiesterase 4 inhibitors**

Phosphodiesterase (PDE) 4 inhibitors inhibit the release of cytokines and chemokines from inflammatory cells via an increase in intracellular cAMP.\textsuperscript{70} Their clinical use is limited in asthma by side-effects, such as nausea. In contrast with corticosteroids, PDE4 inhibitors have a potent inhibitory effect on neutrophils, indicating that they may be useful anti-inflammatory treatments in more severe asthma.

**Nuclear factor-κB inhibitors**

Nuclear factor-κB regulates the expression of many cytokines and chemokines involved in asthma.\textsuperscript{71} There are several possible approaches to inhibition of NF-κB, including gene transfer of the inhibitor of NF-κB (IκB), inhibitors of IκB kinase-2 (IKK2), NF-κB-inducing kinase (NIK) and IκB ubiquitin ligase, which regulate the activity of NF-κB, and the development of drugs that inhibit the degradation of IκB.\textsuperscript{72} One concern about this approach is that effective inhibitors of NF-κB may result in immune suppression and impair host defences, because knockout mice that lack NF-κB proteins succumb to septicemia.\textsuperscript{72} However, there are alternative pathways of NF-κB activation that may be more important in inflammatory disease. Several small molecule inhibitors of IKK2 are now in development.

**P38 mitogen-activated protein kinase inhibitors**

Mitogen-activated protein kinases (MAPK) play a key role in chronic inflammation and several complex enzyme cascades have now been defined. One of these, the p38 MAPK pathway, is involved in the expression of inflammatory cytokines and chemokines.\textsuperscript{73} Small molecule inhibitors of p38 MAPK, such as SB 203580, SB 239063 and RWJ 67657, also known as cytokine synthesis anti-inflammatory drugs (CSAIDS), have now been developed and these drugs have a broad range of anti-inflammatory effects.\textsuperscript{74} There may be issues of safety, because p38 MAPK are involved in host defence. However, it is possible that the inhaled route of delivery may reduce the risk of side-effects.
CONCLUSIONS
There are several specific cytokine and chemokine inhibitors now in development for the treatment of asthma. Inhibition of IL-4 with sIL-4R in asthma showed promising early results, but this was not confirmed in larger trials and IL-13 inhibition is more promising. Anti-IL-5 antibody is very effective at inhibiting peripheral blood and airway eosinophils, but does not appear to be effective in symptomatic asthma. Inhibitory cytokines, such as IL-10, interferons and IL-12, are less promising, because systemic delivery produces side-effects and it may be necessary to develop inhaled delivery systems. Inhibition of TNF-α may be useful in the treatment of severe asthma. Many chemokines are involved in the inflammatory response of asthma and small molecule inhibitors of chemokine receptors are now in development. The CCR3 antagonists are now being developed for the treatment of asthma. Because so many cytokines are involved in these complex diseases, drugs that inhibit the synthesis of multiple cytokines may be more successful. Several such classes of drug are now in clinical development, including PDE4, p38 MAPK and IKK2 inhibitors. The risk of side-effects in these non-specific inhibitors may be reduced by an inhaled route of delivery.

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