Bifunctional drugs for the treatment of asthma and chronic obstructive pulmonary disease

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ABSTRACT Over the last decade, there has been a steady increase in the use of fixed-dose combinations of drugs for the treatment of a range of diseases, including hypertension, cancer, AIDS, tuberculosis and other infectious diseases. It is now evident that patients with asthma or chronic obstructive pulmonary disease (COPD) can also benefit from the use of fixed-dose combinations, including combinations of a long-acting β₂-agonist and an inhaled corticosteroid, and combinations of long-acting β₂-agonists and long-acting muscarinic receptor antagonists. In fact, there are now a number of “triple-inhaler” fixed-dose combinations under development, with the first such triple combination having been approved in India. This use of combinations containing drugs with complementary pharmacological actions in the treatment of patients with asthma or COPD has also led to the discovery and development of drugs having two different primary pharmacological actions in the same molecule, which we have called “bifunctional drugs”. In this review, we discuss the state of the art of these new bifunctional drugs as novel treatments for asthma and COPD that can be categorised as bifunctional bronchodilators, bifunctional bronchodilator/anti-inflammatory drugs and bifunctional anti-inflammatory drugs.

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Bifunctional drugs offer an exciting new approach to the treatment of asthma and COPD
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Background

Asthma and chronic obstructive pulmonary disease (COPD) are common complex inflammatory diseases of the respiratory tract that often require treatment with multiple drug classes [1, 2]. Over the last decade, there has been a steady increase in the use of fixed-dose combinations of two or more drugs for the treatment of a range of conditions including hypertension [3], cancer [4], AIDS [5], tuberculosis [6] and other infectious diseases [7].

It is now clear that the treatment of asthma and COPD can also benefit from the use of fixed-dose combinations of two or more drugs [8]. Today, the treatment of asthma and COPD globally is dominated by the use of inhaled fixed-dose combinations of a long-acting β2-agonist (LABA) and an inhaled corticosteroid (ICS). Inhaled fixed-dose combinations of both short-acting β2-agonists (SABAs) and short-acting muscarinic receptor antagonists (SAMAs), as well as LABAs and long-acting muscarinic antagonists (LAMAs) are also widely used as bronchodilators for the treatment of patients with COPD and more severe asthma. Indeed, there is now a number of inhaled medicines in development containing various combinations of three of these pharmacological classes, so-called triple inhalers [9–11].

These developments in treatment reflect our growing understanding that there is a need to treat both the underlying inflammation and the symptoms of airway obstruction that characterise these conditions. Moreover, the use of multiple drugs in a single inhaler is thought to improve adherence to treatment, as it is well recognised that patients prescribed a bronchodilator and an anti-inflammatory drug as monoinhalers will often stop the anti-inflammatory drug when symptoms improve [12], despite current understanding suggesting that regular use of ICS (at least in patients with asthma) may be necessary to optimise lung function and reduce exacerbations of the disease in the long term [13].

However, the development of formulations to allow the use of more than one drug class in a single inhaler is sometimes challenging, as there are often differences in duration of action of the monocomponents and issues concerning chemical compatibility and stability, as well as galenic challenges relating to the different physiochemical properties of the different drug classes [8]. This is especially so with the development of triple inhalers and, to date, only one such medicine, containing tiotropium bromide, ciclesonide and formoterol fumarate, has been approved, but only in India [11]. However, at present, there is very little information in the scientific literature supporting the use of triple therapy.

An alternative approach to delivering complementary pharmacological activities for the treatment of patients with asthma or COPD is to develop molecules specifically designed to have two distinct primary pharmacological actions based on distinct pharmacophores, which we will term bifunctional drugs. These are not to be confused with drugs that can exhibit multiple mechanisms of action that may all contribute to clinical effectiveness (e.g. glucocorticosteroids, xanthines or statins) as, while it is recognised that some drugs having multiple effects have been the starting point for the development of bifunctional drugs, they were not intentionally developed to have multiple actions via distinct mechanisms. In this article, we have therefore concentrated on reviewing the current status of bifunctional drugs specifically designed to have two mechanisms of action in the same molecule that are in development for the treatment of asthma and/or COPD (table 1).

Bifunctional bronchodilator drugs

It has long been recognised that β2-agonists and muscarinic receptor antagonists improve lung function by distinct pharmacological mechanisms, β2-agonists acting to relax airway smooth muscle irrespective of the cause of the bronchoconstriction and muscarinic receptor antagonists by blocking M3 receptors on airway smooth muscle to limit the actions of the neurotransmitter acetylcholine (ACh) released from parasympathetic nerves innervating the lung [14].

Moreover, β2-agonists can amplify the bronchial smooth muscle relaxation directly induced by the muscarinic antagonist by decreasing the release of ACh via a modulation of cholinergic neurotransmission that involves calcium-activated potassium (KCa) channels rather than adenyl cyclase and subsequent increases in intracellular levels of cAMP. Activation of KCa channels is thought to hyperpolarise the cell membrane, thus causing reductions in the concentration of intracellular calcium and ACh release in pre-junctional parasympathetic nerves [14, 15], and thus potentially providing additional bronchodilation above the effects seen with antagonism of muscarinic receptors on the airway smooth muscle. However, this mechanism seems unlikely to contribute in a significant way in practice as there is evidence clearly indicating that β2-agonists facilitate, rather than inhibit, parasympathetic ACh release in the airways [16, 17]. Therefore, it has been suggested that crosstalk between muscarinic receptors and β2-adrenoceptors, leading to greater functional antagonism at the level of the airway smooth muscle, may be of more importance in providing any additional bronchodilation when both classes of drug are used together [16, 17]. In effect, crosstalk between Gq-coupled M3 receptors and Ga-coupled β2-adrenoceptors may have a
TABLE 1 Bifunctional drugs that have been evaluated or are under development for treating asthma and/or chronic obstructive pulmonary disease

<table>
<thead>
<tr>
<th>Class/agent</th>
<th>Stage of development</th>
<th>Pros</th>
<th>Cons</th>
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<tbody>
<tr>
<td><strong>MABAs</strong></td>
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<tr>
<td>GSK961081</td>
<td>Phase III</td>
<td>A single molecule that confers both therapeutic effects can avoid the approval of each component separately as well as in combination, and may be a faster and less expensive route to regulatory approval.</td>
<td>The ratio of muscarinic antagonism and β2-agonism activities cannot be adjusted as needed and this limits dosing flexibility. The combination of muscarinic antagonism and β2-agonism activities might theoretically cause a downregulation of β2-adrenergic receptors and an upregulation of muscarinic acetylcholine receptors. Not clear whether the drug should be dosed for the β2 agonist activity or the muscarinic receptor antagonist activity.</td>
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<tr>
<td>AZD2115</td>
<td>Phase II</td>
<td></td>
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<td>LAS190792</td>
<td>Phase I</td>
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<tr>
<td>THRO200495</td>
<td>Preclinical</td>
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<td>TE3352</td>
<td>Preclinical</td>
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<td>PF3429281</td>
<td>Preclinical</td>
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<tr>
<td>PFG438235</td>
<td>Discontinued</td>
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<tr>
<td><strong>Inhaled nitric oxide-donating analogues</strong></td>
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<tr>
<td>TPI 1020</td>
<td>Discontinued</td>
<td>Improved anti-inflammatory effects compared to budesonide (TPI 1020)</td>
<td>Limited clinical efficacy.</td>
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<tr>
<td>NCX 950</td>
<td>Discontinued</td>
<td>Improved bronchodilator effects compared to salbutamol due to the release of NO (NCX 950).</td>
<td>There are concerns about the potential cardiovascular toxicity of PDE3 inhibition. Further studies are needed to better understand the full potential of this novel therapy for COPD and asthma.</td>
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<td><strong>PDE3/4 inhibitors</strong></td>
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<td>RPL554</td>
<td>Phase II</td>
<td>The combination of both bronchodilator (PDE3 mediated) and anti-inflammatory activity (PDE4 mediated) could result in an enhanced overall efficacy profile compared with selective PDE4 inhibitors.</td>
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<tr>
<td>KCA-1490</td>
<td>Preclinical</td>
<td>PDE3 (which is predominantly localised to the particulate cellular fraction) and PDE4 (which is predominantly cytosolic) can regulate different pools of cAMP.</td>
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<td><strong>Other bifunctional PDE inhibitors</strong></td>
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<td>Dual PDE4 inhibitor/β2-agonist</td>
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<tr>
<td>GS-5759</td>
<td>Preclinical</td>
<td>The combination of both anti-inflammatory (PDE4 mediated) and bronchodilator (mediated by β2-agonism or M3-receptor antagonism) activity could result in an enhanced overall efficacy profile compared with selective PDE4 inhibitors.</td>
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<td>Hybrids that combine both salmeterol and the PDE4 inhibitors roflumilast or phthalazine</td>
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<tr>
<td>Dual PDE4 inhibitor/ M3-receptor antagonist</td>
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<tr>
<td>UCB-101333-3</td>
<td>Discontinued</td>
<td>Reduce the IL-4-dependent rise in serum IgE, and reduce IL-13-dependent BHR, lung inflammation, mucin gene expression and serum chitinase responses in mice</td>
<td>Different studies and different agents can produce different effects.</td>
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<td><strong>IL-4/IL-13 dual antagonists</strong></td>
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<td>Dupilumab</td>
<td>Phase II</td>
<td>Might provide robust efficacy in the treatment of asthma and other Th2-driven diseases</td>
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<td>AMG 317</td>
<td>Phase II</td>
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<tr>
<td>Pitrakinra</td>
<td>Phase II</td>
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<td><strong>Notes</strong></td>
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MABA: muscarinic antagonist/β2-agonist; PDE: phosphodiesterase; IL: interleukin; BHR: bronchial hyperresponsiveness; Th: T-helper cell.

major influence on β2-agonist-induced relaxation, presumably by activation of protein kinase C and subsequent phosphorylation of the β2-adrenergic receptor and/or Gi protein that could contribute to the beneficial bronchodilatory effects of dual bronchodilator therapy [16, 17].

Endothelin (ET)-1 is a potent constrictor of airway smooth muscle and may exert various pro-fibrotic effects in the airways. Recent findings have demonstrated that human lung fibroblasts are fully able to respond to ET-1 in a functional autocrine and paracrine way, as well as expressing preproendothelin and processing this to active ET-1 [18]. Human fibroblasts also express functional ET receptors that can regulate the effects in the airways. Recent findings have demonstrated that human lung fibroblasts are fully able to respond to ET-1 in a functional autocrine and paracrine way, as well as expressing preproendothelin and processing this to active ET-1 [18]. Human fibroblasts also express functional ET receptors that can regulate the effects in the airways. Recently, human fibroblasts can also express both muscarinic receptors and β2-receptors. As muscarinic upregulation of ET-1 contributes to profibrotic effects of muscarinic stimuli and β2-agonists have been reported to inhibit the synthesis of ET-1 [19], it is plausible that LABAs and LAMAs could have a long-term benefit on ET-1 expression and thus fibrotic events, although studies have yet to be undertaken to see if this effect seen in vitro translates into a real clinical benefit.

β2-agonists and antimuscarinic drugs have also been demonstrated to inhibit transforming growth factor (TGF)-β1-mediated neutrophilic inflammation in COPD [20]. It is known that TGF-β1 is increased in induced sputum samples from COPD patients compared with healthy controls and that such samples are able to induce neutrophil adherence to bronchial epithelial cells, which is in part TGF-β1 dependent [20]. It is of interest, therefore, that tiotropium bromide has been demonstrated to attenuate neutrophilic inflammation in COPD and that such an effect might be increased by combing with a LABA such as olodaterol [20].
These complementary activities have led to LABAs and LAMAs often being used together, particularly in the treatment of patients with COPD [21]. Additionally, it is recognised that these two classes of drug can provide better bronchodilation than using either class of drug alone (as described above), which is part of the justification for using both classes of drug at the same time [21]. Such observations have therefore led to the development of a number of new drugs that have both $\beta_2$-agonist activity and muscarinic receptor antagonism in the same molecule, some of which have now reached early clinical development [10, 22]. These are referred to as bifunctional (or dual-pharmacophore) muscarinic antagonist/$\beta_2$-agonist (MABA) agents, exemplified by the drug GSK 961081, which has recently been shown to induce bronchodilation in patients with COPD that lasts for up to 24 h, and that is comparable to a combination of salmeterol and tiotropium [22, 23]. While there was improvement in lung function, there did not appear to be any interaction at the level of adverse effects, which would appear to one of the potential major advantages of the MABAs over increasing the dose of a single class of bronchodilator. Other examples of MABAs include THRX 200495, AZD 2115, LAS 190792, TEI3252, PF-3429281 and PF-4348235 (table 1).

The MABA approach circumvents the potential problem of formulating different drugs in one inhaler, providing a fixed ratio of muscarinic antagonism and $\beta_2$-agonism compared with combination therapy [24]. However, what is not yet clear is the relative contribution of the two different pharmacological activities to the overall improvement in lung function observed, and indeed on which pharmacological action such drugs should be optimally dosed, as some examples of MABAs have different pharmacodynamic half-lives for their $\beta_2$-agonist activity and the muscarinic receptor antagonist activity with the same molecule [24, 25]. However, a recent clinical study has demonstrated that treatment with three separate doses of GSK 961081 (once-daily doses of 100 $\mu$g, 400 $\mu$g or 800 $\mu$g, or twice-daily doses of 100 $\mu$g, 200 $\mu$g or 400 $\mu$g) showed superior improvements in lung function in patients with COPD compared with a standard dose of salmeterol (50 $\mu$g twice daily), suggesting that the MABA provides a better treatment than monotherapy with a $\beta_2$-agonist [26]. In fact, differences between GSK 961081 doses and salmeterol treatment ranged from 78 mL (100 $\mu$g once daily) to 200 mL (800 $\mu$g once daily), with statistically significant differences in favour of GSK 961081 for all doses tested, except 100 $\mu$g once daily [26]. To date, however, a similar trial has not yet been performed comparing a MABA with monotherapy with an antimuscarinic drug. Thus, while MABAs show promise, there is much still to be understood as to how best to use these drugs and how they will compare to existing fixed-dose combination inhalers [27].

**Bifunctional bronchodilator/anti-inflammatory drugs**

Xanthines such as theophylline have been widely used as treatments for both asthma and COPD for more than 100 years, and while early clinical studies with such drugs have stressed their bronchodilator activity, they were originally introduced into clinical practice to treat an inflammatory renal disease, glomerular nephritis [28]. Early on, it was recognised experimentally that xanthines could exhibit anti-inflammatory activity in the lung, additional to their bronchodilator activity [29], which has now been confirmed clinically by a number of laboratories in patients with asthma [30–34] or COPD [35, 36]. Such observations demonstrated that it was possible to have both bronchodilator and anti-inflammatory activity in a single molecule. However, theophylline is usually administered systemically (orally for maintenance therapy and intravenously for treatment of acute exacerbations) and it is well known as a drug having a narrow therapeutic window [37]. Furthermore, it is now appreciated that higher doses of theophylline are probably required to obtain the bronchodilator activity than the anti-inflammatory activity, albeit that the latter effect is often only seen following chronic treatment [37, 38]. Additionally, the withdrawal of xanthines from patients with asthma or COPD leads to worsening of airway inflammation and symptoms, even in patients taking glucocorticosteroids and other classes of bronchodilator drug [39–41], suggesting that xanthines possess other useful pharmacological properties not shared with glucocorticosteroids or other bronchodilator classes.

There has therefore been an interest in finding safer xanthines over the years, including bamiphylline [42], enprofylline [43], isbufylline [44] and doxophylline [45, 46], some of which have been approved for the treatment of asthma and COPD. Like theophylline, each of these drugs has been shown to possess anti-inflammatory and bronchodilator actions to varying degrees, and in the case of doxophylline, a wider therapeutic window than theophylline [45]. However, what still remains unclear is the mechanism(s) of action of xanthines that contributes to their anti-inflammatory and bronchodilator activity.

One prominent mechanism of action proposed for xanthines over the last few decades has been inhibition of phosphodiesterase (PDE) enzymes and theophylline and the related xantine isobutyl methylxanthine in particular, have often been described as the archetypal nonselective PDE inhibitors [47]. Therefore, one approach to try and improve the therapeutic window of xanthines has been to develop more selective inhibitors of the growing family of PDEs, as it is now recognised that PDE 3 and 4 are found in airway smooth muscle, and PDE 3, 4 and 7 are found in the majority of inflammatory cells thought to be involved
in the pathogenesis of asthma and COPD [37, 38]. Specifically, the PDE3 isoenzyme is considered to predominate functionally in airway smooth muscle and inhibition of this enzyme, rather than PDE4 inhibition, leads to airway smooth muscle relaxation, whereas the PDE4 isoenzyme is the predominant isoenzyme in the majority of inflammatory cells, including neutrophils, which are implicated in the pathogenesis of COPD, and eosinophils, which characterise inflammation in asthma [37, 38]. As a consequence, a number of PDE4 inhibitors have been shown to have an anti-inflammatory activity clinically [38, 48, 49], which is thought to contribute to a long-term improvement in lung function and fewer exacerbations in patients with severe COPD, as has been observed with the recently approved PDE4 inhibitor, roflumilast N-oxide [50, 51], although the side-effect profile of this drug still limits the wider use of this agent. However, while PDE4 is found in human airway smooth muscle, it is now clear from a number of clinical studies with a variety of PDE4 inhibitors administered either orally [52, 53] or by inhalation [54], that this drug class is not able to induce acute bronchodilation [38]. In contrast, a number of selective PDE3 inhibitors have been shown to be bronchodilators in man [55, 56] and, indeed, recently, PDE3 has been documented to be upregulated in airway smooth muscle obtained from patients with asthma [57].

The recognition that PDE4 inhibitors are anti-inflammatory and PDE3 inhibitors are bronchodilators has led to the development of drugs having dual inhibitory activity for both PDE3 and PDE4 in order to obtain both bronchodilator and anti-inflammatory activity in the same molecule. The first of these was zardaverine, which clearly exhibited bronchodilation in patients with asthma, but unfortunately was halted during clinical development because of gastrointestinal side effects [58]. Another example was benzafentrine (AH 21–132) [59], which was also demonstrated to be a bronchodilator, but was later discontinued from clinical development, as was pumafentrine [60].

More recently, some newer compounds having both PDE3 and 4 inhibitory activities have been described, but these have also been stopped at the preclinical stage because of unwanted gastrointestinal side-effects [61]. However, another novel inhaled PDE3/4 inhibitor, RPL 554 [62], has been shown in early clinical studies to have both bronchodilator and anti-inflammatory actions at the same dose without having significant side-effects [63], representing a potentially new class of drug for the treatment of patients with asthma or COPD [64].

A further attempt to combine anti-inflammatory and bronchodilator actions in a single molecule has been to combine the bronchodilator actions of nitric oxide with the anti-inflammatory actions of an ICS. NO-budesonide (TPI 1020) [65, 66] was the first example of such a drug, but this drug was dropped from further development because of limited clinical efficacy. Another approach attempted to combine nitric oxide and salbutamol into a single molecule (NCX 950) to obtain both bronchodilator and anti-inflammatory actions, which showed some promise pre-clinically [67] (table 1).

GS-5759 is a novel bifunctional PDE4 inhibitor/LABA that displays PDE4 inhibition and β2-agonism comparable to roflumilast and indacaterol, respectively [68]. More recently, a series of molecules that combine the anti-inflammatory PDE4 inhibitor roflumilast with the LABA salmeterol [68] have been described that is another potential example of a new drug class that combine anti-inflammatory and bronchodilator actions in a single molecule, although to date, there are very limited biological data on these molecules. A potential advantage of these compounds is that both β2-agonists and PDE4 inhibitors rely on modulation of the second messenger cAMP to elicit their effects, and it is possible that the combination could provide additive or synergistic anti-inflammatory activity in the lung [69]. In addition, bifunctional compounds in which a PDE4 inhibitor is connected to a muscarinic receptor antagonist have been described [70]. All use a pyrazolopyridine as the PDE4 inhibitor and a biaryl-containing muscarinic antagonist, but differ in the linker [71]. Another molecule with such dual activity is UCB-101333-3, a 4,6-diaminopyrimidine [72].

**Bifunctional anti-inflammatory drugs**

Glucocorticosteroids are currently recognised as the gold standard anti-inflammatory drugs for the treatment of respiratory diseases, in part because they exhibit a wide range of anti-inflammatory actions, including the activation and recruitment of most inflammatory cell types into the lung [73]. However, this drug class can also be associated with significant side-effects when they enter the systemic circulation, as well as having local side-effects when applied topically. Not surprisingly, therefore, given the success of glucocorticosteroids as anti-inflammatory drugs, it has been the ‘holy grail’ of the pharmaceutical industry for many years to find an alternative anti-inflammatory drug to glucocorticosteroids in the respiratory field, but that have a better safety profile [73, 74]. There have been many new classes of anti-inflammatory drug developed [73, 74], most of which have failed, except in the treatment of a subset of more severe patients with asthma [75] or COPD [51]. Many of these have been drugs or biologics directed against a single
inflammatory mediator, and these failures [76–79] suggest that the complexity of the inflammatory response in both asthma and COPD requires drugs that have actions at more than one biological target. Thus, a number of drugs have been developed having bifunctional anti-inflammatory activity, including drugs exhibiting antagonism for the receptors for platelet-activating factor and histamine, and mast cell secretion-blocking effects in the same molecule, such as rupatadine [80, 81]. Another example of bifunctional anti-inflammatory compounds is drugs behaving as thromboxane receptor antagonists and cysteinyl-leukotriene antagonists in the same molecule [82]. However, both of these classes of drug have, to date, only shown limited efficacy, at least in the treatment of allergic airway disease.

There have also been attempts to create bifunctional drugs by dual targeting combinations of cytokines with antibodies. One example is a biologic agent targeting both murine IL-4 and IL-13 that was generated by combining well-characterised binding domains in an optimal configuration, using appropriate linker regions [83]. The bifunctional IL-4 and IL-13 antagonist demonstrated high affinity for both cytokines, and reduced the IL-4-dependent rise in serum IgE, and reduced IL-13-dependent airway hyperresponsiveness, lung inflammation, mucin gene expression and serum chitinase responses in mice. Effective dual blockade of IL-13 and IL-4 resulted in greater therapeutic benefit than was achieved by targeting either cytokine alone [83], and clinical trial results of such an approach are awaited with interest.

Conclusions

It is now apparent that there is a growing trend to develop drugs with bifunctional activity for the treatment of patients with asthma or COPD. Such drugs have the potential benefit of being easier to formulate than combinations of multiple drugs in a single inhaler, improving adherence and the potential to offer additive or even synergistic benefit, as such drugs may target different cellular compartments than when individual drugs are presented to cells separately. It is also likely that the development of bifunctional drugs may serve as a basis for improved “triple-therapy” fixed-dose combination inhalers through co-formulation that could deliver three complementary therapeutic effects for patients with COPD using only two drugs; for instance, there is recent evidence that the use of the dual PDE3/4 inhibitor RPL554 in combination with an M3 muscarinic antagonist may provide synergistic activity on the relaxation of human airway smooth muscle, which suggests that if this drug was combined with an anticholinergic drug, this could translate into further clinical benefit [84]. Furthermore, the MABA GSK961081 has recently been evaluated as twice-daily, fixed-dose combination with fluticasone propionate [10].

We are of the opinion, therefore, that bifunctional drugs offer an exciting new approach to the treatment of asthma and COPD, where there remains significant unmet need, and such drugs could become highly significant future treatments for patients suffering from these common respiratory diseases.

References


