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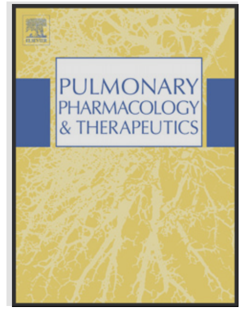

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PDE4-inhibitors: a novel, targeted therapy for obstructive airways disease

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Summary

Roflumilast is a selective once daily, oral phosphodiesterase-4 inhibitor that has recently been registered in all European Union countries as novel targeted therapy for COPD, while FDA approval for the USA market is expected in 2011. In several phase III trials in patients with moderate to (very) severe COPD and in patients with symptoms of chronic bronchitis and recurrent exacerbations, roflumilast showed sustained clinical efficacy by improving lung function and by reducing exacerbation rates. These beneficial effects have also been demonstrated when added to long-acting bronchodilators (both LABA and LAMA), underscoring the anti-inflammatory activity of roflumilast in COPD. Pooled data analysis showed overall mild to moderate, mostly self-limiting adverse events, mainly consisting of nausea, diarrhea and weight loss. In this review we discuss the results of the 4 registration studies showing promising effects of roflumilast in COPD and provide an overview of the topics that still need to be addressed.

keywords: PDE4-inhibitor, roflumilast, clinical trials, chronic obstructive airways disease

Introduction 1

Chronic obstructive airways disease (COPD) represents a heterogeneous group of disorders, 2 characterized by chronic inflammation of the proximal and the distal airways with features of airway remodeling and destruction [1, 2]. These features present as fixed airway obstruction, hyperinflation, dyspnea, mucus hypersecretion and chronic cough. In addition, there is an impairment of the overall health status [2]. The morbidity and mortality due to COPD is increasing worldwide [2]. The major cause of COPD is cigarette smoking, although other environmental pollutants may also serve as triggers in susceptible individuals. These insults induce chronic inflammation and remodeling, including structural changes and destruction of alveolar tissue, within the lung [2-5].

The key effector cells within the airway tissue of COPD patients include macrophages, CD8+ T 3 lymphocytes and neutrophils, releasing toxic mediators [2, 5]. The destruction of alveolar tissue (emphysema) is thought to be caused by the release of proteinase (such as matrix metalloproteinase from alveolar macrophages) or as a consequence of an autoimmune response (e.g. CD8+ T lymphocytes) [6]. Chronic airway inflammation may induce several aspects of airway remodeling, exemplified by goblet cell hyperplasia and enlargement of submucosal glands, which contribute to the excessive mucus production in subjects with chronic bronchitis. Peribronchiolar fibrosis in distal airways is another feature of remodeling, which can induce disruption of the parenchymal attachments to small airways promoting collapse on expiration and hyperinflation [3]. More recently, evidence was provided that the abnormalities seen in COPD are not only restricted to the airways, but also systemically present [7].

There is a longstanding consensus that cigarette smoking is the most common etiological 4 factor in COPD [2], and hence, smoking cessation is still the cornerstone in the treatment of COPD. Alternatively, pharmacotherapeutic options for the treatment of COPD are still limited. Whilst the currently advocated treatment with long-acting muscarinic antagonists (LAMA) and/or long acting beta-adrenoceptor agonists (LABA) with or without inhaled corticosteroids (ICS) have been shown to produce temporary improvements in lung function, exercise tolerance and quality of life, the evidence for reducing exacerbations [8] and, consequently, the rate of decline in lung function, is less convincing [2, 9]. Nor do these drugs improve the systemic features of COPD [10]. In contrast, several studies showed that LABAs may increase morbidity and mortality due to cardiac comorbidity in susceptible patients [11, 12]. Consequently, despite maximal treatment, too many COPD patients still remain symptomatic and experience exacerbations [2], indicating that the current treatment options lack sustained efficacy or disease-modifying properties. Hence, there is a large need of therapeutic modalities producing sustained clinical efficacy for a more optimal treatment of COPD. 1

Phosphodiesterase inhibition is an old concept in the treatment of COPD which has been already described by Hirsch and colleagues in 1922 [13]. However, the application of the prototypic non-selective phosphodiesterase (PDE)-inhibitors, aminophylline and theophylline, has been limited by many drug-interactions and a narrow dose-range, causing many dose-dependent, mostly cardiovascular and gastrointestinal side effects. Whilst theophylline may non-selectively target PDE, albeit at high concentrations, recent evidence points to inhibition of phosphoinositide 3 kinase as a target for the anti-inflammatory action of this drug [14]. In the past decade, interest in PDE-inhibitors has revived due to the identification of 11 different isoenzymes (PDE1-11) within the PDE-superfamily. Each isoenzyme has different tissue subdivision and different properties, hence enabling targeted therapy with potentially fewer (systemic) side effects. In particular, in contrast to non-selective PDE-inhibition, there is considerable interest in selectively targeting the PDE4-isoenzyme, which is expressed in inflammatory cells (e.g. neutrophils, macrophages) and structural cells (e.g. fibroblasts, epithelium, sensory nerves, smooth muscle cells) within the lung [15] (Table 1). The presence of the PDE4-isoenzyme in many of the cell types implicated in COPD would make it a promising target for disease modifying therapy, given the strong relationship between chronic airway inflammation and mucus hypersecretion with increased decline in lung function [16]. Most of the (long-term) studies in COPD so far have been performed with the second generation of oral PDE4-inhibitors, cilomilast (Glaxo Smith Kline) and roflumilast (Nycomed), of which roflumilast possesses 2

the best pharmacological profile (once daily dosing) combined with good clinical efficacy with overall 1
mild and self limiting side effects [17]. In this review we will focus on the most recent clinical trials with the PDE4-inhibitor, roflumilast, showing clinical efficacy in patients with COPD.

Early clinical trials with PDE4-inhibitors 2

The functional consequences of inhibiting PDE4 have consistently shown a reduction in activity of 3
several pro-inflammatory and structural cells, involved in the pathophysiology of COPD with several illustrated in Table 1. Translating these observations into disease, PDE4-inhibition could offer a novel approach to anti-inflammatory and/or disease-modifying therapy. Whilst animal models of COPD are limited, there is some evidence showing that inhibition of PDE4 can suppress pro-inflammatory cell recruitment, cytokine and chemokine production and emphysematous changes to the lung [18-20]. However, early clinical trials with PDE4-inhibitors were met with mixed success.

Orally active PDE4-inhibitors, including CDP840 [21] offered some degree of protection 4
against allergen-induced late asthmatic responses. This effect was comparable to previous reports on the ability of chronic treatment with low dose theophylline to inhibit allergen-induced late phase reactions [22]. However, clinical efficacy of the PDE4-inhibitors cilomilast and roflumilast has mainly been studied in COPD.

The PDE4-inhibitor cilomilast was evaluated in a dose finding study in patients with moderate 5
to severe COPD over a relatively short treatment period of 6 weeks, significantly increasing baseline FEV1 by 11% at the end of the study [17] (Table 2). The improvement in baseline lung function developed gradually, suggesting that, unlike current bronchodilators used in COPD, PDE4-inhibitors may modulate lung function by mechanisms unrelated to airway smooth muscle relaxation *per se*. Indeed, in contrast to salbutamol or ipratropium bromide, administration of cilomilast failed to produce an immediate bronchodilator response [23]. This is also consistent with numerous *in vitro*

studies using isolated human bronchial tissues. In these studies, various PDE4-inhibitors appeared to be poor functional antagonists and produced modest relaxation of airway smooth muscle [24-28]. Another longer-term study with cilomilast confirmed the previously observed improvements in lung function and additionally showed a significant reduction in COPD exacerbations and improvements in quality of life scores [29]. The mechanism for these improvements can likely be attributed to an anti-inflammatory activity. In this respect, cilomilast has been shown to reduce the number of several pro-inflammatory cells, implicated in the pathogenesis of COPD, including CD8+T lymphocytes, CD86+ monocytes/macrophages and neutrophils in lung biopsies from subjects with COPD by approximately 40-50% [30]. This incomplete inhibition might account why the improvements in lung function were not maintained over the 12 week course of this study. Other possible explanations for the improvements in lung function, exacerbation rates and quality of life additional to the indirect bronchodilator effect of cilomilast seen in a majority of these clinical trials could be partly attributed to a modulation of sensory nerve function [31, 32]. A consequence of reduced sensory input to the central nervous system would be a decrease in parasympathetic outflow to the airways, a reduction in contraction of airway smooth muscle and submucosal gland secretion, both leading to improvements in airflow and symptoms. Alternatively, the activation of the cystic fibrosis transmembrane receptor (CFTR) via elevating the level of cyclic AMP in airway epithelial cells could promote rehydration of the epithelial periciliary layer thereby facilitating mucociliary clearance of mucus and bacteria [33]. Indeed, PDE4 inhibitors can reduce mucus production and increase ciliary beat frequency of airway epithelial cells [34, 35]. 1

A number of Phase III studies with cilomilast were conducted to provide further clinical efficacy and safety data for regulatory approval by the FDA. However, these large multicentre phase III trials failed to meet their pre-defined efficacy endpoints, showing no significant improvement in lung function following 24 weeks of treatment. In addition, treatment with cilomilast was frequently associated with gastrointestinal side effects, mainly occurring within the first 2 weeks of treatment. 2

Based on these data, approval was not granted and the development of cilomilast was terminated 1
[36].

Two conclusions can be drawn from the failure of cilomilast. Either the hypothesis that 2
targeting PDE4 will be clinically beneficial for the treatment of COPD is flawed or sustained PDE4-inhibition in the lung is required in order to produce any meaningful clinical benefit to the patient. The authors are convinced that the former statement can only be accepted once the second statement has been rejected following rigorous exploration. Evaluation of the clinical efficacy of the PDE4-inhibitor roflumilast, a highly potent, once daily PDE4-inhibitor, provides a useful tool to test this hypothesis.

Roflumilast: pharmacokinetics, clinical efficacy from phase III clinical trials 3

Following oral ingestion, roflumilast is rapidly absorbed with a **t**max of approx 1 h and a 4
bioavailability of around 80%. Over a dose-range of 250-1000 mcg, roflumilast shows linearly dose-proportional pharmacokinetics and the plasma disposition half-life ranges from 10 to 20 h, warranting a once-daily administration. Roflumilast is rapidly metabolized by CYP3A4 and CYP1A2 enzymes. N-oxide, being the major metabolite of roflumilast, possesses selectivity for the PDE4 isoenzymes (but not for PDE4 subtypes) and largely accounts for its effects in humans *in vivo*. Both roflumilast and N-oxide are mainly excreted via the urine. There are no major drug interactions reported between roflumilast and other (COPD-related) pharmacological treatments [37, 38].

The various clinical studies are summarized in Table 2. In the first, double-blind, parallel trial 5
(M2-107), 1411 patients with moderate to severe COPD were randomized to either roflumilast 250 µg (n=576) or roflumilast 500 µg (n=555) or placebo (n=280) once daily during 24 weeks. As compared to placebo, patients in both roflumilast-arms showed improvements in terms of post-bronchodilator FEV1 (p <0.014), health-related quality of life (NS) and the number of COPD-

exacerbations (p=0.0114) [39]. In another study, subjects with moderate to (very) severe COPD 1 (GOLD stages II to IV) received roflumilast for one year, resulting in a small but significant improvement in baseline FEV1, a modest reduction in exacerbation rates in GOLD-stage IV patients, but quality of life scores did not reach statistical significance [40].

Recently, the results of 4 pivotal randomized controlled trials (RCT) with roflumilast in large 2 groups of patients with moderate to severe COPD have been published [41]. Apart from the effect on lung function, the focus of these trials was on the longer-term clinical efficacy of roflumilast based on GOLD-criteria: *i.e.* prevention and treatment of COPD-exacerbations in addition to safety/tolerability. The paper by Fabbri et al. reports the results of 2 clinical studies in COPD evaluating the effects of treatment with roflumilast *versus* placebo in addition to salmeterol (M2-127) or tiotropium (M2-128), respectively [42]. In the first study (M2-127), after a placebo-run-in period of 4 weeks, patients with moderate to severe COPD were randomized to either roflumilast (n=466) or placebo (n=467) treatment in combination with salmeterol during 24 weeks. In the second study (M2-128), patients received either roflumilast (n=371) or placebo (n=372) in combination with tiotropium for 24 weeks [42]. Both studies included patient populations of chronic smokers or ex-smokers (≥10 packyears), none of them using inhaled corticosteroids at randomization. In the M2-128 (tiotropium-combination) study, symptomatic patients with chronic cough and sputum production with frequent use of short-acting bronchodilators were included. In both studies, roflumilast was associated with consistent and sustained improvements in both the pre- and post-bronchodilator FEV1. In the salmeterol-combination, the mean increase in pre-bronchodilator FEV1 *versus* placebo was 49 mL, while in the tiotropium-combination the mean increase mounted to 80 mL, respectively ($p<0.0001$). Furthermore, in both studies, patients on roflumilast tended to have fewer exacerbations. In both studies, the drop-out rate was larger in the roflumilast-arm with significantly more withdrawals in the salmeterol-roflumilast-arm (p=0.0019). The most frequently reported, roflumilast-related side effects consisted of nausea, diarrhea and mild weight loss (mean 1.8 and 2 kg), respectively.

The studies reported by Calverley et al (M2-124 and M2-125, respectively) used an identical study design including chronic smokers or ex-smokers (≥20 packyears) with symptomatic, (very) severe COPD characterized by chronic cough, sputum production and exacerbations [41]. The inclusion criteria were based on a post-hoc analysis of a previous study, suggesting a decrease in exacerbations by roflumilast in this COPD-phenotype [40]. Initially, 44% of the patients were using ICS or LAMA or both: these drugs have been discontinued for the duration of the study (1 year). Concomitant use of short-acting beta2-agonists, short-acting muscarinic antagonists and LABA was allowed and at randomization; patients were stratified according to initial LABA use to allow a pre-specified subgroup analysis. In both studies, after a 4 week placebo-run in period, patients received either roflumilast or placebo for 52 weeks on top of their existing anti-COPD medication. Based on pooled data analysis, in the roflumilast treated-patients, there was a mean increase in pre-bronchodilator FEV1 of 48 mL *versus* placebo ($p<0.0001$). Furthermore, compared to placebo, roflumilast produced a substantial decrease in both moderate and severe exacerbations by on mean 17% ($p<0.0003$). The improvement in lung function and reduction in exacerbations were independent of concomitant use of LABA or short-acting muscarinic antagonists or prior ICS-use or smoking behaviour. The mortality due to COPD was similar in both treatment-arms in both studies (2-3%). Similar adverse events as in the study by Fabbri et al. were reported: i.e. mainly CNS (head ache, insomnia and nausea) and gastrointestinal (diarrhea) complaints. Although mostly selflimiting, these adverse events resulted in premature withdrawal in both roflumilast-arms during the first 4-12 weeks of the study. In addition, roflumilast produced a sustained, mean weight loss of 2.1 kg in mainly obese patients during the first 6 months of use. Roflumilast awaits FDA approval in the USA in 2011 and European registration was obtained mid 2010. 1

The mechanism of the improvements in lung function, exacerbation rates and quality of life scores cannot be attributed to a direct bronchodilating action of this drug class, as we have previously discussed for cilomilast. It is more likely that these beneficial actions are secondary to an anti-inflammatory activity of roflumilast, although the reduction in pro-inflammatory cell numbers 2

found in two other studies was modest, reflecting a 30-50% suppression of inflammatory cell 1
numbers [43, 44] and reduced the number of airway CD8+ T lymphocytes and CD68+ macrophages by approximately 40-50% [30]. Other evidence of an anti-inflammatory mechanism stems from *in vitro* studies which reported that cilomilast reduced the level of TNF-alpha (25% decrease), GMCSF (46% decrease) and neutrophil chemotactic factors (35% decrease) with no effect on IL-8 released by epithelial cells from COPD patients [45]. It remains to be established, whether greater inhibition of the inflammatory response would lead to more impressive improvements in clinical endpoints, including lung function and exacerbation rates.

It is noteworthy that current bronchodilator drugs used in the treatment of COPD have 2
minimal impact on the inflammatory response within the airways. The reduction in exacerbations in COPD-patients treated with tiotropium bromide was not accompanied by a reduction in inflammatory cells or sputum cytokine or chemokine levels [46, 47]. Following treatment with this LAMA, sputum levels of pro-inflammatory mediators tended to rise, which could be a consequence of a reduction in mucus secretion, thereby concentrating the levels of these mediators. However, these changes are unlikely to be clinically relevant in view of their small magnitude (less than 2 fold) and improvements in lung function and reduction in exacerbations seen in large trials (Table 1). In contrast, there is evidence that glucocorticosteroids can reduce airway inflammation in COPD. The number of pro-inflammatory cells (CD3+, CD4+, CD8+ T lymphocytes, macrophages, mast cells) in biopsies from 101 patients previously steroid-naïve (GOLD stages II and III) but who were treated with fluticasone showed a significant reduction in inflammatory cell numbers over a 2.5 year treatment period. As compared to placebo, the magnitude of the reduction in the number of COPD-relevant inflammatory cells in bronchial biopsies was approximately 25% at 6 months and 45 % at 30 months of treatment [48]. More importantly, in this long-term study, there was no evidence of any additive or synergistic anti-inflammatory effect with combination therapy (salmeterol and fluticasone) [48]. In contrast, following combination therapy, there was an improvement in lung function, which was not seen with fluticasone monotherapy [48]. Therefore, the improvements in

FEV1 seen with combination therapy of ICS and LABA can be explained by relaxation of airway smooth muscle rather than a consequence of a synergistic or additive anti-inflammatory action, as evidenced by the comparable changes in rates of decline in lung function between salmeterol *versus* combination therapy [49]. Although earlier studies showed that combination therapy was associated with anti-inflammatory activity [50] after 12-13 weeks of treatment, which may be superior to monotherapy with fluticasone [51], the clinical relevance of these effects is debatable in light of the lack of effect of this treatment on lung function parameters [51]. Interestingly, the effect of fluticasone monotherapy on airway neutrophil numbers is conflicting, with both reports of a reduction [48] and increase [52] and again, the differences could be due to the relatively short duration of treatment in a limited number of patients in these studies. Alternatively, there is evidence of a (relative) corticosteroid resistance in patients with COPD. Although recent studies yielded a number of possible mechanisms to explain this insensitivity, the central hypothesis implies the increase in oxidant burden within the lungs, resulting in reduction in the activity of histone deacetylase (HDAC)-2. Accordingly, increasing the HDAC2-activity by PDE-inhibitors, phosphoinositide 3 kinase-delta inhibitors and macrolides could result in a reversal of corticosteroid resistance [53]. 1

Beyond Roflumilast 2

One of the major issues facing systemically administered PDE4-inhibitors is the potential to also produce nausea and headache as side-effects which have shunted off cilomilast and have not been entirely eliminated for roflumilast. Several strategies are available to avoid such problems. One possibility might be to develop subtype-selective PDE4-inhibitors since it has become dogma that side-effects like nausea are due exclusively to inhibition of the PDE4D isoenzymes - however, this viewpoint in not universally shared [15] and the recent discovery of selective brain-penetrant PDE4- 3 inhibitors that are devoid of emesis [54] adds further weight against avoiding the targeting of PDE4D, particularly as this enzyme subtype is expressed in cells of interest to COPD. 1

An alternative approach is to develop topically active inhibitors which have limited systemic exposure and consequently, side-effects could be avoided and the tolerated dose could be increased to achieve more substantial PDE4-inhibition in the lung. Thus far, two inhaled PDE4-inhibitors have been evaluated in respiratory disease. A highly potent PDE4-inhibitor, UK-500,001 failed to demonstrate any improvement in baseline FEV1 in patients with moderate to severe COPD after 6 weeks of treatment [55]. In contrast, the inhaled PDE4-inhibitor, GSK256066, with low systemic exposure, was shown to attenuate the acute and late phase allergic airway response after 1 week of treatment [56], and whether this drug is clinically effective in COPD remains to be established. 2

Another approach worth considering is the possibility of using mixed PDE-inhibitors for the treatment of COPD. This stems from the notion that PDE4-inhibitors *per se* are relatively poor at inhibiting macrophage function (Table 1), that PDE3 is also present in epithelium and airway smooth muscle and that PDE3-inhibition can produce bronchodilator effects and also promote chloride ion secretion [33]. Mixed PDE-inhibitors can serve to have additive or potentially synergistic actions on cell function [27, 33, 57] and whilst early mixed PDE3/4 inhibitors evaluated by the inhaled route showed limited activity [58, 59] this was attributed to their short retention time within the lung. The development of mixed PDE3/4 inhibitors with long duration of action coupled with anti-inflammatory activity could be of greater utility in COPD [60]. 3

In a similar fashion, it has been suggested that targeting PDE7 may also be beneficial in view of its widespread distribution in various inflammatory and structural airway cell types implicated in the pathogenesis of COPD [61, 62]. However, targeting PDE7 with a chemical inhibitor failed to modify cell function *in vitro*, but when used in combination appeared to enhance the inhibitory action of a PDE4 selective inhibitor [62]. Targeting both PDE4 and PDE7 with antisense oligonucleotides suppressed various indices of airway inflammation in mice exposed to cigarette 4 smoke [20], and whilst combination treatment was not compared with component oligonucleotides against the inflammatory response, it appears that simultaneous targeting of PDE4 and PDE7 provided a greater inhibitory activity than targeting PDE4 only and warrants the development of mixed PDE-inhibitors for the treatment of COPD.

Adverse events during long-term PDE4-inhibition

In contrast to the non-selective PDE-inhibitor theophylline, the second generation selective PDE4-inhibitors cilomilast and roflumilast have been shown to cause substantially less side effects in terms of incidence and severity. In all 6-12 months randomized controlled trials, the most commonly roflumilast-related adverse events, reported by COPD-patients, included central adverse events (nausea, headache, insomnia), gastro-intestinal side effects (diarrhea) and (modest) weight loss [39-42]. Adverse events mostly became evident during the first 4-12 weeks and although usually subsiding with continued treatment, these events caused an increased patient withdrawal in the roflumilast-arms. In addition, no clinically relevant cardiac toxicity was reported in none of the patients [39-42].

In the pooled data analysis of the M2-124/125 studies, the most common side effects were diarrhea and weight loss. The incidence of adverse events was 67% in the roflumilast arm and 65% in the placebo-arm, while serious side effects were noted in 19% and 22% of the patients, respectively. Overall, drop-outs due to side effects occurred more frequently in the roflumilast (14%) *versus* the placebo-arm (11%). In all 4 registration trials (M2-124/125 and M2-127/128) weight loss was reported, with a mean of 2.1 kg, mostly occurring in the first 6 months of the M2-124/125 studies [41] and with a similar mean weight loss of 2.0 and 1.8 kg, respectively, in the M2-127/128 studies [42]. The largest absolute weight loss was seen in patients with a BMI >30. Based on a subanalysis from M2-128, this weight loss could be ascribed primarily to fat loss; how this relates to the systemic anti-inflammatory potential of roflumilast, needs to be clarified [63].

In the COPD safety pooled analysis, including over 12,000 COPD patients from several RCT trials (797 patients on roflumilast 250 µg, 5766 patients on roflumilast 500 µg, 5491 patients on placebo), 3 cases of suicides were reported, all receiving roflumilast treatment (1 on 250 µg, and 2 on 500 µg) [Food and Drug Administration. www.fda.gov/downloads/advisory committees/committeesmeetingmaterials/drugs/pulmonary-allergydrugsadvisorycommittee/UCM207377.pdf]. Despite relatively small numbers and a potentially pre-existent depression among these patients, these findings obviously require close monitoring.

It has recently been highlighted in cell culture experiments that roflumilast, albeit at concentrations that would never be achieved clinically, promoted IL-8 secretion from human endothelial cells and induced neutrophil recruitment to the lungs when administered to mice [64]. Similarly, PDE4-inhibition promoted chemokine expression in monocyte/macrophage in culture [65] suggesting that this drug class might be anticipated to potentially promote inflammation. However, these data are not consistent with numerous studies documenting anti-inflammatory effects of PDE4-inhibitors (Table 1). Indeed, roflumilast treatment alone failed to significantly increase macrophage and neutrophil cell number in the lung in a preclinical model of smoke-induced inflammation, but reduced the rise in macrophage and neutrophil cell numbers caused by cigarette smoke exposure [18, 66]. Similarly, human clinical data shows that the PDE4-inhibitors, cilomilast and roflumilast, reduce inflammatory cell numbers in the lung compartment [43, 67]. In conclusion, ample evidence has been provided that the PDE4-inhibitors cilomilast and roflumilast, at a clinically relevant dose, are capable of reducing airway inflammation.

Conclusions

COPD imposes an increasing burden on mankind, health care and resources. Smoking is the pivotal inducer of COPD, and therefore smoking cessation is the cornerstone in the prevention and treatment of COPD. Despite Global Initiative for COPD, current pharmacological approach to COPD

fails to provide sustained efficacy, while still too many patients experience frequent exacerbations 1
with poor quality of life due to impairment of their general health status and an accelerated decline in lung function. These events contribute to the increasing morbidity and mortality among COPD patients.

In mid 2010, a novel, targeted approach to COPD, has been registered in several European 2
countries, consisting of roflumilast, a once daily oral PDE4-inhibitor. In several 6-12 months RCTs, this selective PDE4-inhibitor has shown sustained clinical efficacy, in terms of clinically relevant bronchodilation and decreases in COPD-exacerbations. In patients with symptomatic (very) severe COPD with chronic cough, sputum and prone to frequent exacerbations, roflumilast caused relief through improvements in lung function and, more importantly, through decrease in exacerbation rates, in addition to their existing anti-COPD therapy. Since the improvements in lung function by roflumilast have been additive to concomitant use of LABA or LAMA, this suggests anti-inflammatory activity. A pooled data analysis showed that the side effects associated with roflumilast (nausea, headache, diarrhea and weight loss) were mostly mild to moderate and usually self-limiting, although resulted in an increased patient withdrawal across the studies.

There are still some outstanding questions that need to be addressed. First: what are the 3
local and systemic anti-inflammatory effects of roflumilast in COPD? Second: to what extent can PDE4-inhibitors reverse corticosteroid resistance? Third: do PDE4-inhibitors (as monotherapy or in combination with ICS) possess disease-modifying properties, in terms of prevention of the increased decline in lung function and/or modulation of the systemic effects in COPD? And, if so, can (combinations with) PDE4-inhibitors decrease the morbidity and mortality of (certain phenotypes of) COPD?

Overall, roflumilast showed promising effects in symptomatic patients across the moderate 4
to (very) severe GOLD-stages. Future trials in these patients should be directed to test clinical efficacy of roflumilast on top of inhaled corticosteroids and to compare clinical efficacy of (LABA-

combinations of) roflumilast and ICS. In addition, studies with roflumilast as monotherapy in other 1
(milder (smoking?)) COPD phenotypes should test its preventive potential. This approach should consequently allow evidence-based positioning of roflumilast in the guidelines of pharmacological COPD management.

References 1

[1] Han MK, Wise R, Mumford J, Sciurba F, Criner GJ, Curtis JL, et al. Prevalence and clinical correlates 2
of bronchoreversibility in severe emphysema. European Respiratory Journal. 2010;35:1048-56.

[2] Rodriguez-Roisin R, Anzeuto A, Bourbeau J, Calverley P, S.deGuia T, Fukuchi Y, et al. Global 3
Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. 2009. p. 1-93.

[3] Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, Buzatu L, et al. The nature of small-airway 4
obstruction in chronic obstructive pulmonary disease. N Engl J Med. 2004;350:2645-53.

[4] Barnes PJ. Mediators of chronic obstructive pulmonary disease. Pharmacol Rev. 2004;56:515-48. 5

[5] Barnes PJ. The cytokine network in asthma and chronic obstructive pulmonary disease. JClin 6
Invest. 2008;118:3546-56.

[6] Tetley TD. Inflammatory cells and chronic obstructive pulmonary disease. Curr Drug Targets 7
Inflamm Allergy. 2005;4:607-18.

[7] Sinden NJ, Stockley RA. Systemic inflammation and comorbidity in COPD: a result of 'overspill' of 8
inflammatory mediators from the lungs? Review of the evidence. Thorax. 2010.

[8] Singh S, Loke YK. An overview of the benefits and drawbacks of inhaled corticosteroids in chronic 9
obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2010;5:189-95.

[9] Celli B, Vestbo J, Jenkins CR, Jones PW, Ferguson GT, Calverley PM, et al. Gender Differences in 10
Mortality and Clinical Expressions of Patients with COPD: The TORCH Experience. Am J Respir Crit Care Med. 2010.

[10] Cazzola M, Molimard M. The scientific rationale for combining long-acting beta2-agonists and 1
muscarinic antagonists in COPD. Pulm Pharmacol Ther. 2010;23:257-67.

[11] Hawkins NM, Wang D, Petrie MC, Pfeffer MA, Swedberg K, Granger CB, et al. Baseline 2
characteristics and outcomes of patients with heart failure receiving bronchodilators in the CHARM programme. Eur J Heart Fail. 2010;12:557-65.

[12] Hawkins NM, Jhund PS, Simpson CR, Petrie MC, Macdonald MR, Dunn FG, et al. Primary care 3
burden and treatment of patients with heart failure and chronic obstructive pulmonary disease in Scotland. Eur J Heart Fail. 2010;12:17-24.

[13] Diamant Z, Boot JD, Virchow JC. Summing up 100 years of asthma. RespirMed. 2007;101:378-88. 4

[14] To Y, Ito K, Kizawa Y, Failla M, Ito M, Kusama T, et al. Targeting phosphoinositide-3-kinase-delta 5
with theophylline reverses corticosteroid insensitivity in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2010;182:897-904.

[15] Page CP, Spina D. PDE inhibitors in the treatment of inflammatory diseases. HandbExp 6
Pharmacol. 2010;(in press).

[16] Vestbo J, Prescott E, Lange P. Association of chronic mucus hypersecretion with FEV1 decline 7
and chronic obstructive pulmonary disease morbidity. Copenhagen City Heart Study Group. AmJRespirCrit Care Med. 1996;153:1530-5.

[17] Compton CH, Gubb J, Nieman R, Edelson J, Amit O, Bakst A, et al. Cilomilast, a selective 8
phosphodiesterase-4 inhibitor for treatment of patients with chronic obstructive pulmonary disease: a randomised, dose-ranging study. Lancet. 2001;358:265-70.

[18] Martorana PA, Beume R, Lucattelli M, Wollin L, Lungarella G. Roflumilast fully prevents 1
emphysema in mice chronically exposed to cigarette smoke. Am J Respir Crit Care Med. 2005;172:848-53.

[19] Leclerc O, Lagente V, Planquois JM, Berthelier C, Artola M, Eichholtz T, et al. Involvement of 2
MMP-12 and phosphodiesterase type 4 in cigarette smoke-induced inflammation in mice. Eur Respir J. 2006;27:1102-9.

[20] Fortin M, D'Anjou H, Higgins ME, Gougeon J, Aube P, Moktefi K, et al. A multi-target antisense 3
approach against PDE4 and PDE7 reduces smoke-induced lung inflammation in mice. RespirRes. 2009;10:39.

[21] Harbinson PL, MacLeod D, Hawksworth R, O'Toole S, Sullivan PJ, Heath P, et al. The effect of a 4
novel orally active selective PDE4 isoenzyme inhibitor (CDP840) on allergen-induced responses in asthmatic subjects. EurRespirJ. 1997;10:1008-14.

[22] Sullivan P, Bekir S, Jaffar Z, Page C, Jeffery P, Costello J. Anti-inflammatory effects of low-dose 5
oral theophylline in atopic asthma [published erratum appears in Lancet 1994 Jun 11; 343(8911):1512]. Lancet. 1994;343:1006-8.

[23] Grootendorst DC, Gauw SA, Baan R, Kelly J, Murdoch RD, Sterk PJ, et al. Does a single dose of the 6
phosphodiesterase 4 inhibitor, cilomilast (15 mg), induce bronchodilation in patients with chronic obstructive pulmonary disease? PulmPharmacolTher. 2003;16:115-20.

[24] Schmidt DT, Watson N, Dent G, Ruhlmann E, Branscheid D, Magnussen H, et al. The effect of 7
selective and non-selective phosphodiesterase inhibitors on allergen- and leukotriene C(4)-induced contractions in passively sensitized human airways. BrJPharmacol. 2000;131:1607-18.

[25] Billington CK, Le Jeune IR, Young KW, Hall IP. A major functional role for phosphodiesterase 4D5 8
in human airway smooth muscle cells. AmJRespirCell MolBiol. 2008;38:1-7.

[26] Rabe KF, Tenor H, Dent G, Schudt C, Liebig S, Magnussen H. Phosphodiesterase isozymes 1
modulating inherent tone in human airways: identification and characterization. AmJPhysiol. 1993;264:L458-L64.

[27] Torphy TJ, Undem BJ, Cieslinski LB, Luttmann MA, Reeves ML, Hay DW. Identification, 2
characterization and functional role of phosphodiesterase isozymes in human airway smooth muscle. JPharmacolExpTher. 1993;265:1213-23.

[28] Grootendorst DC, Gauw SA, Baan R, Kelly J, Murdoch RD, Sterk PJ, et al. Does a single dose of the 3
phosphodiesterase 4 inhibitor, cilomilast (15 mg), induce bronchodilation in patients with chronic obstructive pulmonary disease? Pulm Pharmacol Ther. 2003;16:115-20.

[29] Rennard SI, Schachter N, Strek M, Rickard K, Amit O. Cilomilast for COPD: results of a 6-month, 4
placebo-controlled study of a potent, selective inhibitor of phosphodiesterase 4. Chest. 2006;129:56-66.

[30] Gamble E, Grootendorst DC, Brightling CE, Troy S, Qiu Y, Zhu J, et al. Antiinflammatory effects of 5
the phosphodiesterase-4 inhibitor cilomilast (Ariflo) in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2003;168:976-82.

[31] Undem BJ, Meeker SN, Chen J. Inhibition of neurally mediated nonadrenergic, noncholinergic 6
contractions of guinea pig bronchus by isozyme-selective phosphodiesterase inhibitors. JPharmacolExpTher. 1994;271:811-7.

[32] Spina D, Harrison S, Page CP. Regulation by phosphodiesterase isoenzymes of non-adrenergic 7
non- cholinergic contraction in guinea-pig isolated main bronchus. BrJPharmacol. 1995;116:2334-40.

[33] Liu S, Veilleux A, Zhang L, Young A, Kwok E, Laliberte F, et al. Dynamic activation of cystic fibrosis 8
transmembrane conductance regulator by type 3 and type 4D phosphodiesterase inhibitors. JPharmacolExpTher. 2005;314:846-54.

[34] Cervin A, Lindgren S. The effect of selective phosphodiesterase inhibitors on mucociliary activity in the upper and lower airways in vitro. Auris Nasus Larynx. 1998;25:269-76. 1

[35] Mata M, Sarria B, Buenestado A, Cortijo J, Cerda M, Morcillo EJ. Phosphodiesterase 4 inhibition decreases MUC5AC expression induced by epidermal growth factor in human airway epithelial cells. Thorax. 2005;60:144-52. 2

[36] Rennard S, Knobil K, Rabe KF, Morris A, Schachter N, Locantore N, et al. The efficacy and safety of cilomilast in COPD. Drugs. 2008;68 Suppl 2:3-57. 3

[37] Hatzelmann A, Morcillo EJ, Lungarella G, Adnot S, Sanjar S, Beume R, et al. The preclinical pharmacology of roflumilast--a selective, oral phosphodiesterase 4 inhibitor in development for chronic obstructive pulmonary disease. PulmPharmacolTher. 2010;23:235-56. 4

[38] Gross NJ, Giembycz MA, Rennard SI. Treatment of chronic obstructive pulmonary disease with roflumilast, a new phosphodiesterase 4 inhibitor. COPD. 2010;7:141-53. 5

[39] Rabe KF, Bateman ED, O'Donnell D, Witte S, Bredenbroker D, Bethke TD. Roflumilast--an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial. Lancet. 2005;366:563-71. 6

[40] Calverley PM, Sanchez-Toril F, McIvor A, Teichmann P, Bredenbroeker D, Fabbri LM. Effect of 1-year treatment with roflumilast in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2007;176:154-61. 7

[41] Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. Lancet. 2009;374:685-94. 8

[42] Fabbri LM, Calverley PM, Izquierdo-Alonso JL, Bundschuh DS, Brose M, Martinez FJ, et al. 1
Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. Lancet. 2009;374:695-703.

[43] Grootendorst DC, Gauw SA, Verhoosel RM, Sterk PJ, Hospers JJ, Bredenbroker D, et al. Reduction 2
in sputum neutrophil and eosinophil numbers by the PDE4 inhibitor roflumilast in patients with COPD. Thorax. 2007;62:1081-7.

[44] Hohlfeld JM, Schoenfeld K, Lavae-Mokhtari M, Schaumann F, Mueller M, Bredenbroeker D, et al. 3
Roflumilast attenuates pulmonary inflammation upon segmental endotoxin challenge in healthy subjects: a randomized placebo-controlled trial. PulmPharmacolTher. 2008;21:616-23.

[45] Profita M, Chiappara G, Mirabella F, Di Giorgi R, Chimenti L, Costanzo G, et al. Effect of cilomilast 4
(Ariflo) on TNF-alpha, IL-8, and GM-CSF release by airway cells of patients with COPD. Thorax. 2003;58:573-9.

[46] Powrie DJ, Wilkinson TMA, Donaldson GC, Jones P, Scrine K, Viel K, et al. Effect of tiotropium on 5
sputum and serum inflammatory markers and exacerbations in COPD. European Respiratory Journal. 2007;30:472-8.

[47] Perng DW, Tao CW, Su KC, Tsai CC, Liu LY, Lee YC. Anti-inflammatory effects of 6
salmeterol/fluticasone, tiotropium/fluticasone or tiotropium in COPD. European Respiratory Journal. 2009;33:778-84.

[48] Lapperre TS, Snoeck-Stroband JB, Gosman MME, Jansen DF, Van Schadewijk A, Thiadens HA, et 7
al. Effect of fluticasone with and without salmeterol on pulmonary outcomes in chronic obstructive pulmonary disease. Ann Intern Med. 2009;151:517-27.

[49] Calverley PMA, Anderson JA, Celli BR, Ferguson GT, Jenkins CR, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356:775-89. 1

[50] Barnes NC. Antiinflammatory Effects of Salmeterol/Fluticasone Propionate in Chronic Obstructive Lung Disease. American Journal of Respiratory and Critical Care Medicine. 2006;173:736-43. 2
3

[51] Bourbeau J, Christodoulopoulos P, Maltais F, Yamauchi Y, Olivenstein R, Hamid Q. Effect of salmeterol/fluticasone propionate on airway inflammation in COPD: a randomised controlled trial. Thorax. 2007;62:938-43. 4

[52] Gizycki MJ. Effects of fluticasone propionate on inflammatory cells in COPD: an ultrastructural examination of endobronchial biopsy tissue. Thorax. 2002;57:799-803. 5

[53] Barnes PJ. Mechanisms and resistance in glucocorticoid control of inflammation. J Steroid Biochem Mol Biol. 2010;120:76-85. 6

[54] Burgin AB, Magnusson OT, Singh J, Witte P, Staker BL, Bjornsson JM, et al. Design of phosphodiesterase 4D (PDE4D) allosteric modulators for enhancing cognition with improved safety. NatBiotechnol. 2010;28:63-70. 7

[55] Vestbo J, Tan L, Atkinson G, Ward J. A controlled trial of 6-weeks' treatment with a novel inhaled phosphodiesterase type-4 inhibitor in COPD. EurRespirJ. 2009;33:1039-44. 8

[56] Singh D, Petavy F, Macdonald AJ, Lazaar AL, O'Connor BJ. The inhaled phosphodiesterase 4 inhibitor GSK256066 reduces allergen challenge responses in asthma. RespirRes. 2010;11:26-35. 9

[57] Selige J, Tenor H, Hatzelmann A, Dunkern T. Cytokine-dependent balance of mitogenic effects in primary human lung fibroblasts related to cyclic AMP signaling and phosphodiesterase 4 inhibition. JCell Physiol. 2010;223:317-26. 1

[58] Brunnee T, Engelstatter R, Steinijans VW, Kunkel G. Bronchodilatory effect of inhaled zardaverine, a phosphodiesterase III and IV inhibitor, in patients with asthma. EurRespirJ. 1992;5:982-5. 2

[59] Ukena D, Rentz K, Reiber C, Sybrecht GW. Effects of the mixed phosphodiesterase III/IV inhibitor, zardaverine, on airway function in patients with chronic airflow obstruction. Respir Med. 1995;89:441-4. 3

[60] Boswell-Smith V, Spina D, Oxford AW, Comer MB, Seeds EA, Page CP. The pharmacology of two novel long-acting phosphodiesterase 3/4 inhibitors, RPL554 [9,10-dimethoxy-2(2,4,6-trimethylphenylimino)-3-(n-carbamoyl-2-aminoethyl) -3,4,6,7-tetrahydro-2H-pyrimido[6,1-a]isoquinolin-4-one] and RPL565 [6,7-dihydro-2-(2,6-diisopropylphenoxy)-9,10-dimethoxy-4H-pyrimido[6,1-a]i soquinolin-4-one]. J Pharmacol Exp Ther. 2006;318:840-8. 4

[61] Wright LC, Seybold J, Robichaud A, Adcock IM, Barnes PJ. Phosphodiesterase expression in human epithelial cells. American Journal of Physiology - Lung Cellular & Molecular Physiology. 1998;275:L694-L700. 5

[62] Smith SJ, Brookes-Fazakerley S, Donnelly LE, Barnes PJ, Barnette MS, Giembycz MA. Ubiquitous expression of phosphodiesterase 7A in human proinflammatory and immune cells. Am J Physiol Lung Cell Mol Physiol. 2003;284:L279-L89. 6

[63] Wouters EFM, Teichmann P, Brose M, Rabe KF, Fabbri LM. Effects of roflumilast, a phosphodiesterase 4 inhibitor, on body composition in chronic obstructive pulmonary disease. Am J Respir Cell Mol Biol. 2010;181:A4473. 7

[64] McCluskie K, Klein U, Linnevers C, Ji YH, Yang A, Husfeld C, et al. Phosphodiesterase type 4 1
inhibitors cause proinflammatory effects in vivo. J Pharmacol Exp Ther. 2006;319:468-76.

[65] Hertz AL, Bender AT, Smith KC, Gilchrist M, Amieux PS, Aderem A, et al. Elevated cyclic AMP and 2
PDE4 inhibition induce chemokine expression in human monocyte-derived macrophages. Proceedings of the National Academy of Sciences. 2009;106:21978-83.

[66] Martorana PA, Lunghi B, Lucattelli M, De CG, Beume R, Lungarella G. Effect of roflumilast on 3
inflammatory cells in the lungs of cigarette smoke-exposed mice. BMCPulmMed. 2008;8:17.

[67] Gamble E, Pavord ID, Vignola AM, Kroegel C, Morell F, Hansel TT, et al. Cilomilast reduces CD8+ 4
T-lymphocytes and macrophages in patients with chronic obstructive pulmonary disease (COPD): a double-blind placebo-controlled, parallel-group quantitiative study of bronchial biopsies. Eur Respir J. 2001;17:P2238.

[68] Gantner F, Tenor H, Gekeler V, Schudt C, Wendel A, Hatzelmann A. Phosphodiesterase profiles of 5
highly purified human peripheral blood leukocyte populations from normal and atopic individuals: a comparative study. JAllergy ClinImmunol. 1997;100:527-35.

[69] Hatzelmann A, Schudt C. Anti-inflammatory and immunomodulatory potential of the novel PDE4 6
inhibitor roflumilast in vitro. JPharmacolExpTher. 2001;297:267-79.

[70] Peter D, Jin SL, Conti M, Hatzelmann A, Zitt C. Differential expression and function of 7
phosphodiesterase 4 (PDE4) subtypes in human primary CD4+ T cells: predominant role of PDE4D. J Immunol. 2007;178:4820-31.

[71] Essayan DM, Kagey-Sobotka A, Lichtenstein LM, Huang SK. Differential regulation of human 8
antigen-specific Th1 and Th2 lymphocyte responses by isozyme selective cyclic nucleotide phosphodiesterase inhibitors. Journal of Pharmacology & Experimental Therapeutics. 1997;282:505-
12. 9

[72] Ma R, Yang BY, Wu CY. A selective phosphodiesterase 4 (PDE4) inhibitor Zl-n-91 suppresses IL-17 1 production by human memory Th17 cells. IntImmunopharmacol. 2008;8:1408-17.

[73] Gantner F, Gotz C, Gekeler V, Schudt C, Wendel A, Hatzelmann A. Phosphodiesterase profile of 2 human B lymphocytes from normal and atopic donors and the effects of PDE inhibition on B cell proliferation. BrJPharmacol. 1998;123:1031-8.

[74] Parkkonen J, Hasala H, Moilanen E, Giembycz MA, Kankaanranta H. Phosphodiesterase 4 3 inhibitors delay human eosinophil and neutrophil apoptosis in the absence and presence of salbutamol. Pulm Pharmacol Ther. 2007.

[75] Jones NA, Boswell-Smith V, Lever R, Page CP. The effect of selective phosphodiesterase 4 isoenzyme inhibition on neutrophil function in vitro. Pulm Pharmacol Ther. 2005;18:93-101.

[76] Heystek HC, Thierry AC, Soulard P, Moulon C. Phosphodiesterase 4 inhibitors reduce human 5 dendritic cell inflammatory cytokine production and Th1-polarizing capacity. Int Immunol. 2003;15:827-35.

[77] Barber R, Baillie GS, Bergmann R, Shepherd MC, Sepper R, Houslay MD, et al. Differential 6 expression of PDE4 cAMP phosphodiesterase isoforms in inflammatory cells of smokers with COPD, smokers without COPD, and nonsmokers. Am J Physiol Lung Cell Mol Physiol. 2004;287:L332-L43.

[78] Gantner F, Kupferschmidt R, Schudt C, Wendel A, Hatzelmann A. In vitro differentiation of 7 human monocytes to macrophages: Change of PDE profile and its relationship to suppression of tumour necrosis factor-alpha release by PDE inhibitors. British Journal of Pharmacology. 1997;121:221-31.

[79] Weston MC, Anderson N, Peachell PT. Effects of phosphodiesterase inhibitors on human lung 8 mast cell and basophil function. BrJPharmacol. 1997;121:287-95.

[80] Shichijo M, Inagaki N, Nakai N, Kimata M, Nakahata T, Serizawa I, et al. The effects of anti-asthma drugs on mediator release from cultured human mast cells. Clin Exp Allergy. 1998;28:1228-36. 1 2

[81] Fuhrmann M, Jahn HU, Seybold J, Neurohr C, Barnes PJ, Hippenstiel S, et al. Identification and function of cyclic nucleotide phosphodiesterase isoenzymes in airway epithelial cells. AmJRespirCell MolBiol. 1999;20:292-302. 3

[82] Haddad JJ, Land SC, Tarnow-Mordi WO, Zembala M, Kowalczyk D, Lauterbach R. Immunopharmacological potential of selective phosphodiesterase inhibition. I. Differential regulation of lipopolysaccharide-mediated proinflammatory cytokine (interleukin-6 and tumor necrosis factor-alpha) biosynthesis in alveolar epithelial cells. JPharmacolExpTher. 2002;300:559-66. 4

[83] Sanz MJ, Cortijo J, Taha MA, Cerda-Nicolas M, Schatton E, Burgbacher B, et al. Roflumilast inhibits leukocyte-endothelial cell interactions, expression of adhesion molecules and microvascular permeability. Br J Pharmacol. 2007;152:481-92. 5

[84] Suttorp N, Ehreiser P, Hippenstiel S, Fuhrmann M, Krull M, Tenor H, et al. Hyperpermeability of pulmonary endothelial monolayer: protective role of phosphodiesterase isoenzymes 3 and 4. Lung. 1996;174:181-94. 6

[85] Kohyama T, Liu X, Zhu YK, Wen FQ, Wang HJ, Fang Q, et al. Phosphodiesterase 4 inhibitor cilomilast inhibits fibroblast-mediated collagen gel degradation induced by tumor necrosis factor-alpha and neutrophil elastase. Am J Respir Cell Mol Biol. 2002;27:487-94. 7

[86] Martin-Chouly CA, Astier A, Jacob C, Pruniaux MP, Bertrand C, Lagente V. Modulation of matrix metalloproteinase production from human lung fibroblasts by type 4 phosphodiesterase inhibitors. Life Sci. 2004;75:823-40. 8

[87] Dunkern TR, Feurstein D, Rossi GA, Sabatini F, Hatzelmann A. Inhibition of TGF-beta induced lung 1
fibroblast to myofibroblast conversion by phosphodiesterase inhibiting drugs and activators of soluble guanylyl cyclase. Eur J Pharmacol. 2007;572:12-22.

[88] Sabatini F, Petecchia L, Boero S, Silvestri M, Klar J, Tenor H, et al. A phosphodiesterase 4 2
inhibitor, roflumilast N-oxide, inhibits human lung fibroblast functions in vitro. PulmPharmacolTher. 2010;23:283-91.

[89] Noh AL, Yang M, Lee JM, Park H, Lee DS, Yim M. Phosphodiesterase 3 and 4 negatively regulate 3
receptor activator of nuclear factor-kappaB ligand-mediated osteoclast formation by prostaglandin E2. BiolPharmBull. 2009;32:1844-8.

[90] Tenor H, Hedbom E, Hauselmann HJ, Schudt C, Hatzelmann A. Phosphodiesterase isoenzyme 4
families in human osteoarthritis chondrocytes--functional importance of phosphodiesterase 4. BrJPharmacol. 2002;135:609-18.

[91] Waddleton D, Wu W, Feng Y, Thompson C, Wu M, Zhou YP, et al. Phosphodiesterase 3 and 4 5
comprise the major cAMP metabolizing enzymes responsible for insulin secretion in INS-1 (832/13) cells and rat islets. Biochem Pharmacol. 2008;76:884-93.

[92] Wang H, Edens NK. mRNA expression and antilipolytic role of phosphodiesterase 4 in rat 6
adipocytes in vitro. JLipid Res. 2007;48:1099-107.

[93] Snyder PB, Esselstyn JM, Loughney K, Wolda SL, Florio VA. The role of cyclic nucleotide 7
phosphodiesterases in the regulation of adipocyte lipolysis. J Lipid Res. 2005;46:494-503.

[94] Tashkin DP, Celli BR, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4 year trial of tiotropium in 8
chronic obstructive pulmonary disease. N Engl J Med. 2007;359:1543-54.

[95] Aaron SD, Vandemheen KL, Ferguson EW, Maltals F, Bourbeau J, Goldstein R, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease. Ann Intern Med. 2007;146:545-55. 1

[96] Szafranski W, Cukier A, Ramirez A, Menga G, Sansores R, Nahabedian S, et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. European Respiratory Journal. 2003;21:74-81. 2

Table 1. PDE-distribution within human cells of interest for the treatment of chronic obstructive airway disorders, including COPD and persistent asthma

Cell type	PDE4 Subtype[1]	Other PDE's	Biological consequence of PDE- inhibition	Reference
T lymphocytes				
CD4		3, 7	Inhibition of proliferation and cytokine release	[57, 63-67]
CD8	A, B, D*			
Th1, Th2, Th17				
B Cells	A, B, D	7	Increased proliferation	[57, 68]
Eosinophils	A, B, D	7	Inhibition of superoxide anion generation; Delayed apoptosis	[57, 64, 69]
Neutrophils	A, B, D	7	Inhibition of superoxide anion and neutrophil elastase release	[57, 64, 70]
Monocyte	A, B, D	7	Inhibition of TNFα release	[57, 64, 70, 71]
Macrophages	A, B, D	1,3,7	Inhibition of TNFα release**	[57, 64, 72, 73]
Dendritic cells	A, B, D	1,3	Inhibition of TNFα release	[64, 71]
Osteoblast	A, B, D	3	Stimulates RANKL-induced osteoclast formation	[74]
Chondrocytes	A, B, D	1	Inhibition of IL-1β stimulated production of nitric oxide	[75]
Mast Cells			Little if any mast cell stabilization	[76, 77]
Airway epithelial cells		1-3,4, 5, 7,8	Increased production of PGE_2; inhibition of IL-6 production; increase ion efflux	[31, 56, 78, 79]
Endothelial cells		2,3,4,5	Inhibition of adhesion molecule expression	[70, 80]
Fibroblasts	A, B, D	1,4,5,7	Inhibition of fibroblast chemotaxis; inhibition of pro-MMP1,2 release; differentiation into myofibroblasts; inhibition of cytokine & chemokine production; inhibition of expression of alpha smooth muscle actin; inhibition of fibroblast proliferation	[52, 57, 81-84]

[2]Sensory nerves	D	1,3	Inhibition of neuropeptide release	[29, 30]

*PDE4D absent in Th1 cells 1

** In the presence of a PDE3 inhibitor

[1]PDE4 subtype mRNA expression illustrating relative abundance in cells

[2]Guinea-pig sensory nerves

Table 2. A summary of the most important clinical trials with PDE4 inhibitors and long acting bronchodilators in COPD.

Duration of treatment	Treatment Groups	Severity‡	Endpoints	Results	Reference
6 weeks	Placebo (106/89) Cilomilast 5 mg bid (109/92) Cilomilast 10 mg bid (102/85) Cilomilast 15 mg bid (107/89)	54 %	Prebronchodilator FEV1 SGRQ score	160 mL increase over placebo 3.9 units cf placebo† (NS)	[16]
24 weeks	Placebo (216/208) Cilomilast 15 mg bid (431/394)	49 %	Prebronchodilator FEV1 SGRQ score Exacerbations	40 mL increase over placebo 4.1 units cf placebo 39% decrease	[27]
24 weeks	Placebo (280/248) Roflumilast 0.25 mg (578/478) Roflumilast 0.5 mg (555/431)	50 %	Prebronchodilator FEV1 Postbronchodilator FEV1 SGRQ score	64 and 88 ml increase over placebo, respective to dose. 74 and 97 ml increase over placebo, respective to dose. 1.7 units cf placebo†	[35]

			Exacerbations	34 % decrease	
52 weeks	Placebo (753/590) Roflumilast 0.5 mg od (761/544)	40 %	Prebronchodilator FEV1 Postbronchodilator FEV1 SGRQ score Exacerbations: (GOLD IV)	36 ml increase over placebo 39 ml increase over placebo 3 units cf placebo† 36% lower	[36]
24 weeks (M2-127)	Placebo (467/385) Rolfumilast 0.5 mg od (466/359) Salmeterol both groups	50 %	Prebronchodilator FEV1 Postbronchodilator FEV1 Mean rate of exacerbations (mild, moderate, severe) Dyspnea index	49 ml increase over placebo/salmeterol 60 ml increase over placebo/salmeterol NS cf placebo/salmeterol NS cf placebo/salmeterol	[38]
24 weeks (M2-128)	Placebo (372/333) Rolfumilast 0.5 mg od (371/309) Tiotropium both groups	50 %	Prebronchodilator FEV1 Postbronchodilator FEV1 Mean rate of exacerbation (mild, moderate, severe) Dyspnea index (TDI focal	80 ml increase over placebo/tiotropium 81 ml increase over placebo/tiotropium NS cf placebo/tiotropium 0.4 units/2.6 units significantly better	[38]

1

			score/ change in SOBQ)	with roflumilast	
52 weeks (M2-124)	Placebo (758/524) Roflumilast (765/501)	42%	Prebronchodilator FEV1 Postbronchodilator FEV1 Moderate to severe exacerbation rate per patient	39 ml increase over placebo 49 ml increase over placebo 15 % lower incidence	[37]
52 weeks (MS-125)	Placebo (796/548) Roflumilast (772/526)	41 %	Prebronchodilator FEV1 Postbronchodilator FEV1 Moderate to severe exacerbation rate per patient	58 ml increase over placebo 61 ml increase over placebo 18 % lower incidence	[37]
4 years	Placebo (3006/1648) Tiotropium (2987/1887)	43 %	Prebronchodilator FEV1 Postbronchodilator FEV1 Mean number of exacerbations	87 – 103 ml increase over placebo 47 – 65 ml increase over placebo 14 % decrease compared with placebo	[85]

1

			Rate of decline in lung function SGRQ	NS compared with placebo 2.7 units cf placebo (P < 0.001)	
52 weeks	Tiotropium (156/82) Tiotropium and salmeterol (148/84) Triple combination (145/108)	43 %	Prebronchodilator FEV1 Exacerbations Hospitalizations SGRQ Dyspnea	27 ml increase in Tio/placebo group and NS vs Tio/salmeterol 86 ml increase in Tio/salmeterol/fluticasone group and P = 0.049 vs Tio/placebo NS difference between groups Combination therapy reduced incidence compared with tiotropium alone. Tio/placebo (-4.5 units) vs Tio/salmeterol (-6.3 units; P = 0.02) and vs Tio/salmeterol/fluticasone(-8.6 units; P = 0.01) NS difference between groups	[86]

3 years	Placebo (1524/851) Salmeterol (1521/960) Fluticasone proprionate (1534/947) Combination (1533/1011)		Postbronchodilator FEV1 Exacerbations Mortality (COPD related) SGRQ	Salmeterol = 42 ml; Fluticasone = 47 ml; Combination = 92 ml vs placebo 25 % reduction (combination vs placebo) 15 % reduction (salmeterol vs placebo) 18 % reduction (fluticasone vs placebo) SFC NS compared with placebo Salmeterol (-1) vs placebo (NS) Fluticasone (-2) and Combination (-3.1) vs placebo (P < 0.001)	[45]
52 weeks	Placebo (205/115) Formoterol (201/137) Budesonide (198/136) Combination (208/149)	43 %	Prebronchodilator FEV1 Exacerbations SGRQ	Formoterol = 140 ml; Budesonide = 50 ml; Combination = 150 ml above placebo Combination treatment reduced mean severe exacerbation rate vs placebo and formoterol (24 % and 23 %, respectively) Combination, budesonide, formoterol and placebo (-3.9, -1.9, -3.6, -0.03 respectively). Combination significantly better than placebo (P = 0.009)	[87]

1

Unless otherwise specified all comparisons are statistically significant.

†SGRQ scores above 4 are considered clinically relevant

‡ FEV1/FVC average across groups;

SGRQ: St George's Respiratory Questionnaire; SOBQ; shortness of breath questionnaire; RR = rate ratio

Values in parentheses represented number of subjects randomized to each treatment group (assigned/completed).

TDI; transition dyspnea index