

Are phosphodiesterase 4 inhibitors just more theophylline?

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Theophylline has been relegated to a second- or even third-line therapy in the treatment of asthma and chronic obstructive pulmonary disease (COPD), behind glucocorticosteroids and β_2 -agonists, although recent findings have suggested that theophylline possesses anti-inflammatory and immunomodulatory effects in addition to its well-recognized effects as a bronchodilator. In part, theophylline has fallen out of favor because of its adverse side-effect profile, and this has led to the search for more effective and safer drugs based on the knowledge that theophylline is orally active and that it is a nonselective phosphodiesterase (PDE) inhibitor. This has led to the development of selective PDE4 inhibitors, originally designed for depression, for the treatment of both COPD and asthma. Such drugs have shown clinical efficacy in the treatment of respiratory disease while having a considerably safer side-effect profile in comparison with theophylline, particularly because there are no reported drug interactions with PDE4 inhibitors, a feature that complicates the use of theophylline. In addition, it is also becoming increasingly apparent that theophylline is not working solely through PDE inhibition, as formerly assumed, and that this drug has other relevant pharmacologic activities that are likely to contribute to its efficacy, such as adenosine receptor antagonism and induction of histone deacetylase. Thus, the introduction of PDE4 inhibitors represents an entirely new class of drugs for the treatment of respiratory disease. (*J Allergy Clin Immunol* 2006;117:1237-43.)

Key words: Theophylline, phosphodiesterase 4 inhibitors, chronic obstructive pulmonary disease, asthma

Abbreviations used

cAMP: Cyclic 3',5' adenosine monophosphate
cGMP: Cyclic 3',5' guanosine monophosphate
COPD: Chronic obstructive pulmonary disease
HARBS: High-affinity rolipram-binding sites
LARBS: Low-affinity rolipram-binding sites
PDE: Phosphodiesterase

Isoenzyme-selective phosphodiesterase (PDE) inhibitors have garnered widespread attention in recent years for their potential to treat a wide range of diseases, including the chronic lung diseases, asthma and chronic obstructive pulmonary disease (COPD). Their initial development for lung disease was in part instigated to try and improve the efficacy and therapeutic index of the orally active methylxanthine theophylline. Theophylline has been used to treat asthma and COPD for more than 75 years, and its clinical effects have long been thought to be due to bronchodilatation, although it is now known to exhibit some anti-inflammatory actions. The predominant mechanism of action of theophylline has traditionally been ascribed to nonselective PDE inhibition, but there is increasing evidence that some of its clinical effects might be due to other mechanisms of action. This review discusses the mechanism of action and clinical effects of theophylline and PDE inhibitors and asks whether PDE4 inhibitors are just improved theophylline.

THEOPHYLLINE

Since the first prescription of theophylline for the treatment of asthma in 1937, it has been widely used as an inexpensive oral treatment of both asthma and COPD.¹ Traditional dogma has attributed the therapeutic effect of theophylline primarily to bronchodilatation, but at lower concentrations, it also possesses both immunomodulatory and anti-inflammatory actions, which are likely to contribute to some of the efficacy of the drug in treating patients with pulmonary disease.²

However, prescriptions of theophylline have been decreasing in recent years in most developed countries, and it has now been relegated to a second- or even third-line asthma therapy.³ This is mainly due to the introduction

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of newer drugs, such as the long acting β_2 -agonists and inhaled glucocorticosteroids, given alone or in combination, which have both improved efficacy and a better side-effect profile than theophylline. Nevertheless, theophylline has the distinct advantage of being able to be administered orally and is still used in the management of patients with severe asthma who appear to be steroid resistant, and a number of clinical trials have shown that patients with moderate asthma (FEV_1 of approximately 70% of predicted value) can derive more benefit from combined theophylline and glucocorticosteroid therapy than by increasing steroid dosing.^{4,5} In patients with COPD, theophylline is normally only used as a bronchodilator, either alone or in combination with long-acting β_2 -agonists or anticholinergic agents in patients with moderate (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage II) or more severe (GOLD stages III-IV) disease.⁶

The limitations and side effects of theophylline result from its narrow therapeutic index, traditionally between 10 and 20 $\mu\text{g}\cdot\text{mL}^{-1}$ in plasma, although the recommended dose has now been reduced to approximately 5 to 15 $\mu\text{g}\cdot\text{mL}^{-1}$, and it is now prescribed as a slow-release formulation to try and alleviate some of its problems. Another problem of theophylline is that it is metabolized in the liver through the cytochrome P450 system and consequently is implicated in a number of unwanted drug interactions with other commonly prescribed drugs, including cimetidine, erythromycin, and calcium-channel blockers, all of which increase serum concentrations of theophylline. Conversely, drugs such as phenytoin and carbamazepine can decrease serum concentrations of theophylline. Careful prescribing is required to prevent occurrence of such drug interactions, thereby making theophylline a difficult drug to manage, particularly in children and the elderly, who tend to have impaired metabolic pathways. However, theophylline remains a useful drug and is one of the few orally active drugs available for the treatment of asthma, which is particularly pertinent because patients consistently demonstrate a preference for orally administered compounds over those administered through other routes.⁷

Despite its extensive use in the treatment of respiratory disease, the precise molecular actions of theophylline have not been fully elucidated. Traditionally, its efficacy in the treatment of patients with COPD or asthma has been attributed to nonselective PDE inhibition.⁸ However, it has been demonstrated that theophylline administered at therapeutic plasma levels (10 $\mu\text{g}\cdot\text{mL}^{-1}$) only exerts a very modest nonselective inhibition of PDEs, which might not be clinically relevant,¹ and at the lower doses now recommended, which have been shown to have significant anti-inflammatory activity, there is little evidence that theophylline inhibits any of the known PDE enzyme families. A number of other potential mechanisms of action of theophylline have therefore been proposed, including adenosine receptor antagonism⁹ and increasing histone deacetylase activity.¹⁰

Nonetheless, the positive clinical effects of theophylline in airways disease, combined with its advantageous oral bioavailability, has spurred the development of highly

selective PDE inhibitors for the treatment of respiratory disease, with the anticipation that such drugs would have greater efficacy than theophylline but with an improved side-effect profile.

CLASSIFICATION OF PDEs

Eleven PDE families have now been identified by a variety of criteria, including substrate specificity, inhibitor potency, genetic makeup, and enzyme kinetics.^{11,12} They act by hydrolyzing the phosphodiester bond of the second messengers cyclic nucleotides—cyclic 3',5' adenosine monophosphate (cAMP) and cyclic 3',5' guanosine monophosphate (cGMP), converting them to the inactive 5' mononucleotides AMP and guanosine monophosphate, respectively.¹³ cAMP and cGMP are key second messengers in regulating inflammatory cell function, and therefore PDEs can influence a large number of pharmacologic processes, including inflammatory mediator production, cellular differentiation and apoptosis, smooth muscle contraction, ion-channel function, and glycogenesis. Each PDE family is populated by between 1 and 4 gene products, giving rise to a large number of isoforms, many of which have distinct cellular and subcellular distribution.¹² The functional significance of this tightly regulated distribution of PDE enzymes is currently unclear,¹¹ but it does allow for specific targeting of isoforms in cells and tissues implicated in disease. The most successful result of this thus far has been the introduction of the PDE5-selective inhibitors, such as sildenafil, for the treatment of erectile dysfunction¹⁴ and, more recently, pulmonary hypertension.¹⁵ Table I shows a summary of the PDE families, with some example inhibitors.

PDE4: A THERAPEUTIC TARGET IN COPD AND ASTHMA

The PDE4 isoenzyme was identified as a major therapeutic target in respiratory diseases because it is the predominant isoenzyme in the majority of inflammatory cells, including neutrophils, which are implicated in the pathogenesis of COPD,¹⁶ and eosinophils, which characterize inflammation in asthma.¹⁷ PDE4 is also present alongside the PDE3 isoenzyme in airway smooth muscle; the PDE3 isoenzyme is considered to predominate in airway smooth muscle, and inhibition of this enzyme, rather than PDE4, inhibition of which leads to airway smooth muscle relaxation.¹³ A wide range of *in vitro* and *in vivo* studies have demonstrated the ability of PDE4 inhibitors to regulate activation of relevant cells implicated in airways disease, and Table II¹⁸⁻³⁵ summarizes the various effects PDE4 inhibitors can exhibit on human inflammatory and resident cell function.

PDE4 is encoded by 4 genes, each of which generates a number of isoforms that can be divided into subfamilies (PDE4A-D). The expression and subcellular localization of these isoforms varies enormously between tissues and cells.³⁶ It is hypothesized that the tightly regulated

TABLE I. An overview of the PDE families

PDE family	K _m (μM)		Specific inhibitors		Theophylline
	cAMP	cGMP	Name	IC ₅₀	IC ₅₀
1. Ca ²⁺ /calmodulin stimulated	1-30	3	—	—	>100
2. cGMP stimulated	50	50	EHNA	83 μM	>100
3. cGMP inhibited	0.2	0.3	Cilostamide	0.1 μM	>100
			Milrinone	0.5 μM	—
			Siguazodan	1-3 μM	—
4. cAMP specific	4	>1000	Rolipram	0.21 μmol/L	1642 μM (4a)
			Roflumilast	0.0008 μmol/L	—
			Cilomilast	0.12 μmol/L	—
5. cGMP specific	150	1	Sildenafil	0.7 nM	>100
			Vardenafil	6.6 nM	—
6. Photoreceptor	60	>100	Zaprinast	—	>100
7. High-affinity cAMP specific	0.2	>100	NA	—	343.5 (7a)
8. High-affinity cAMP specific	0.055	124	NA	—	>100
9. High-affinity cGMP specific	230	0.17	NA	—	>100
10. Unknown	0.05	3	NA	—	>100
11. Unknown	1.04	0.52	NA	—	>100

K_m, Affinity of an enzyme for its substrate; IC₅₀, inhibitory concentration of 50%; EHNA, erythro-9-(2-hydroxy-3-nonyl) adenine; NA, not applicable.

expression of PDE4 isoforms in subcellular domains can closely regulate the level of cAMP in the locality of effector proteins, including nuclear factor κB, p38 mitogen-activated protein kinase, and c-Jun N-terminal kinase³⁷ and are therefore thought to be involved in cell function control.^{11,12} Changes in PDE4 isoform expression are also hypothesized to occur in chronic inflammatory disease, and therefore the different isoforms might have differential functional importance in normal and disease states.^{38,39}

The clinical development of first-generation PDE4-selective inhibitors, such as rolipram, was hampered by dose-limiting side effects of nausea and vomiting, and therefore various strategies were undertaken to try and improve the side-effect profiles of these drugs. It has been hypothesized that differential binding of inhibitors to PDE4 subtypes might be important in the adverse effects of PDE4 inhibitors. For example, the PDE4C subtype is not found in significant amounts in inflammatory cells and might contribute to some of the side effects associated with these drugs,³⁶ although a recent study showed that this enzyme was upregulated in a rat model of inflammation, suggesting it could play a significant role in inflammatory conditions.⁴⁰ Furthermore, the PDE4D subtype is associated with emesis in mice⁴¹ and has been localized to areas within the central nervous system of monkeys associated with emesis.⁴² In contrast, early studies have indicated that the PDE4B subtype is associated with inflammation,⁴³ although there is evidence that the PDE4B and PDE4D subtypes are nonredundant at sites of inflammation.¹⁸ These data suggest that selective targeting of PDE4B over PDE4D might contribute to an improved side-effect profile. Cilomilast, a PDE4-selective inhibitor, shows 10-fold selectivity toward PDE4D compared with PDE4A and PDE4B,⁴⁴ whereas roflumilast, another PDE4 inhibitor in clinical development, shows selectivity toward the PDE4B and PDE4D subtypes. Nevertheless, although these are better tolerated than rolipram,

TABLE II. The *in vitro* effects of PDE4 inhibitors

Cell	Study	Reference
Mast cell	Decrease IgE-mediated degranulation	20
T lymphocytes	Suppress proliferation	21
Neutrophil	Reduce IL-8 and LTB ₄ production	22,23
	Reduce ROS	19
	Reduce CD11b expression	24
	Decrease chemotaxis	24
	Suppress neutrophil elastase and MMP-9 release	24
Eosinophil	Decrease ROS and LTC ₄ production	26
Macrophage and monocyte	Decrease TNF-α, LTC ₄ , and LTB ₄ production	18
	Increase IL-10 production	27
		28
Epithelium	Decrease IL-6 and TNF-α production	29
	Increase PGE ₂ production	30
	Decrease EGF-induced MUC5AC expression	29
Dendritic cells	Decrease TNF-α production	22
Endothelial cells	Decrease adhesion molecule expression and lymphocyte transmigration	32
T lymphocyte	Suppress IL-2, IL-4, IL-5, and IFN-γ production	21
	Suppress proliferation	33
		34
Sensory nerves	Suppress EFS-induced eNANC	35

LT, Leukotriene; ROS, reactive oxygen species; MMP-9, matrix metalloproteinase 9; PG, prostaglandin; EGF, epidermal growth factor; EFS, electrical field stimulation; eNANC, excitatory nonadrenergic noncholinergic.

gastrointestinal side effects are still observed with these drugs. Another factor that might be significant in the adverse side effects seen with PDE4 inhibitors is their relative affinity for the high-affinity rolipram-binding sites (HARBS) and low-affinity rolipram-binding sites

TABLE III. A selection of PDE4 inhibitors in current development

Drug	Drug company	Development stage	PDE4 Inhibitors IC ₅₀	PDE4 subselectivity	Reference
Roflumilast	Altana	Phase III	0.9 nM	PDE4 B and D	48
Cilomilast	GlaxoSmithKline	Phase III	122 nM	PDE4 D	45
AWD12-281	Elbion AG	Phase II	9.71 nM	None	49
NVP-ABE171	Novartis	Preclinical	A 602 nM B 34 nM C 230 nM D 1.5 nM	PDE4 B and D	50
GRC-3886	Glenmark	Phase I	—	—	46
V11294	Purdue/Napp	Phase I	405 nM	—	51
HT0712	Inflazyme	Phase I	—	—	47

IC₅₀, Inhibitory concentration of 50%.

(LARBS) conformation of the PDE4 enzyme, which has been suggested to play a crucial role in terms of tolerability and efficacy of PDE4 inhibitors.⁴⁵ Marked binding affinity to HARBS predominantly relates to adverse events, which might explain the high rate of nausea observed in a COPD trial with cilomilast.¹⁹ In contrast, a more balanced binding of PDE4 inhibitors to LARBS and HARBS is exerted by roflumilast, which could account for the reduced incidence of nausea (3.2%) seen with this drug.⁴⁶ However, both HARBS and LARBS binding have been associated with the anti-inflammatory effects of PDE4 inhibitors, and therefore selective binding of one over the other might not prove to be efficacious. Table III⁴⁵⁻⁵¹ comprises a list of PDE4 inhibitors currently in development, which now includes 2 early-stage drugs that are claimed not to cause nausea or emesis in healthy volunteers.^{47,52}

Roflumilast (Daxas), developed by Altana AG (Bad Homburg, Germany), and cilomilast (Ariflo), developed by GlaxoSmithKline (Uxbridge, United Kingdom), are currently the most advanced PDE4 inhibitors undergoing clinical trials for airways disease. In a placebo-controlled trial consisting of 1411 patients with COPD, 500 µg once daily of roflumilast produced a significant improvement in postbronchodilator FEV₁, whereas exacerbations were reduced by 34% over placebo.⁴⁸ In the same group of patients, roflumilast was found to be safe and well tolerated, although the class-associated side effects of diarrhea, nausea, and headache were still apparent.⁴⁸ A study investigating sputum samples of 36 patients with COPD after 4 weeks of treatment with roflumilast, 500 µg once daily, showed a significant reduction in the amount-number of neutrophils and eosinophils,⁵³ thus adding clinical evidence to the wide range of anti-inflammatory effects observed in preclinical studies. In a multicenter, placebo-controlled, 6-month study of 647 patients with COPD, cilomilast (15 mg twice daily) also resulted in an improvement in FEV₁ compared with placebo ($P = .002$). There was also a clinically significant improvement in the St George's Respiratory Questionnaire score and a greater percentage of exacerbation-free weeks in cilomilast-treated patients.¹⁹ These data demonstrate that PDE4 inhibitors can improve clinical symptoms in patients with COPD, although unlike theophylline, they have no direct bronchodilator activity⁵⁴ and are therefore

likely to be having a different mechanism of action. In addition, in a murine model roflumilast has also been shown to prevent the development of cigarette smoke-induced emphysema, suggesting that it could be used as a protective therapy in smokers to prevent deterioration of their lung function, although this has yet to be explored clinically.⁵⁵

A trial in asthmatic patients showed that 7 to 10 days of treatment with roflumilast (250 or 500 µg once daily) could reduce early asthmatic reactions and late asthmatic reactions after allergen challenge⁵⁶; an earlier trial observed a reduction of airway hyperresponsiveness and the late asthmatic reaction after a single 1000-µg dose of roflumilast. The pronounced suppression of late responses in allergen challenge models suggests a clinically relevant anti-inflammatory activity of roflumilast at doses that can be safely administered in the clinic. In a 12-week study of 456 asthmatic patients, treatment with roflumilast (100, 250, and 500 µg once daily) produced a significant (11% to 16%) increase in baseline FEV₁,⁵⁷ and in a follow-up study in which all patients were administered 500 µg of roflumilast once daily for 40 weeks, lung function improvements were found to be maintained for the duration of the study in patients previously administered 250 and 500 µg once daily. In those patients who had previously been treated with 100 µg of roflumilast once daily, a significant improvement in their lung function was observed after the dose was increased.⁵⁸ Interestingly, 500 µg of roflumilast once daily has also been shown to produce significant improvements in peak expiratory flow in patients with asthma after just 1 day, with continuing improvements throughout the 12 weeks of the study,⁵⁹ although in other studies an acute effect was not observed 6 hours after application of a single dose of roflumilast⁶⁰ or cilomilast.⁶¹ In addition, in most clinical trials with oral PDE4 inhibitors, a maximum level of lung function improvement was attained within the first 2 to 4 weeks of treatment,⁴⁸ providing further evidence of a nonbronchodilator mode of action of PDE4 inhibitors. Another study compared the effects of roflumilast with those of the inhaled corticosteroid beclomethasone dipropionate. In this study 499 asthmatic patients were randomly given either 500 µg of roflumilast once daily or 400 µg of beclomethasone dipropionate twice daily

TABLE IV. Comparison between PDE4 inhibitors and theophylline

PDE4 inhibitors	Theophylline
Suppression of the PDE4 enzyme (and respective subtypes A-D) only	Adenosine receptor antagonism (A_1 and A_2), histone deacetylase activity stimulation, weak unspecific PDE inhibition ¹ Very narrow therapeutic index ($5\text{--}20\text{ }\mu\text{g}\cdot\text{mL}^{-1}$)
Cardiac safety proved (roflumilast) ⁴⁶	Adverse cardiac effects caused by adenosine antagonism (arrhythmias)
Neurologic safety proved (roflumilast) ⁴⁶	Adverse neurologic effects caused by adenosine antagonism (seizures)
No known drug interactions (roflumilast)	Interactions with many drugs, including cimetidine, phenytoin, erythromycin, ciprofloxacin, calcium-channel blockers, fluconazole, rifampin, phenobarbital, and propranolol
No known food interactions	High protein diet has been demonstrated to increase theophylline clearance by 30%
No monitoring of plasma levels necessary	Monitoring of plasma levels obligatory
Sustained plasma levels and efficacy in smokers	Smoking increases theophylline clearance by 40% to 60% and decreases plasma levels and efficacy
No rebound effects after withdrawal of roflumilast therapy but gradual decrease similar to ICS ⁶⁰	Known rebound of lung function decrease below placebo comparison level 32 h after withdrawal of theophylline treatment ⁶³

ICS, Inhaled corticosteroids.

through a metered-dose inhaler for 12 weeks. At the end of the study, both groups of patients had significant and comparable improvements in FEV₁, forced vital capacity, and peak expiratory flow and converse reductions in asthma symptoms and β_2 -agonist use.⁶²

These encouraging clinical studies show that PDE4 inhibitors are able to produce significant clinical improvements in patients with COPD and asthma. Their oral route of administration might enhance patient compliance compared with inhaled glucocorticosteroids and allow the drug to reach systemic sites of relevance to these inflammatory diseases, particularly in patients with COPD. Future investigations should also determine whether systemic application of PDE4 inhibitors might exert beneficial effects on cardiac and other systemic comorbidities frequently observed in patients with COPD. In addition, the major clinical effect of PDE4 inhibitors is anti-inflammatory rather than bronchodilatory, which is the predominant clinical effect of theophylline. PDE4 inhibitors will also be easier to manage with other medications because unlike theophylline, roflumilast has no known drug interactions. Furthermore, the pharmacokinetics of theophylline are known to be affected by smoking and food intake, which has not been observed with PDE4 inhibitors. A full comparison of theophylline and PDE4 inhibitors is shown in Table IV.^{1,46,60,63} However, there are still tolerability issues surrounding PDE4 inhibitors that have not fully been resolved, with a relatively high number of adverse events, particularly gastrointestinal intolerance, seen in patients given PDE4 inhibitors. Furthermore, there is also a major concern surrounding the possibility that PDE4 inhibitors can induce arteriopathy in human subjects, a condition that has been observed in animal models, both rodents⁶⁴ and, more recently, primates,⁶⁵ after high doses of some PDE4 inhibitors. Nonetheless, there is no evidence of PDE4 inhibitors inducing arteriopathy in human subjects, and high doses of theophylline have also been shown to induce arteriopathy in animal models, with no evidence of this occurring in a clinical setting.⁶⁶

CONCLUSION

Therapeutically, PDE4 inhibitors represent a novel class of orally active drugs for the treatment of respiratory disease, with no need to monitor plasma levels, reliable efficacy (even in current smokers), and fewer concerns from drug interactions, although the gastrointestinal side effects do give rise to some concerns regarding their use. However, given the positive effects of roflumilast in comparison with those of inhaled beclomethasone dipropionate,⁶² such drugs might be oral alternatives to inhaled glucocorticosteroids in asthmatic patients whose symptoms are not managed adequately with the current medication. In the treatment of COPD, PDE4 inhibitors might evolve as an interesting therapeutic alternative with potential advantages over inhaled steroids because of the broader anti-inflammatory profile and oral application and the possibility of addressing both the pulmonary and systemic aspects of the disease. Compared with theophylline, treatment with the new PDE4 inhibitors does offer sustained improvement of lung function both in asthma and COPD, accompanied by a higher level of safety and tolerability. At this time, none of the PDE4 inhibitors have gained regulatory approval either in Europe or the United States, although as more progress into the clinic is made, this situation is expected to change, and it is anticipated that PDE4 inhibitors will represent a novel class of orally active drugs for the treatment of respiratory disease.

REFERENCES

1. Barnes PJ. Theophylline: new perspectives for an old drug. *Am J Respir Crit Care Med* 2003;167:813-8.
2. Sullivan P, Bekir S, Jaffar Z, Page C, Jeffery P, Costello J. Anti-inflammatory effects of low-dose oral theophylline in atopic asthma. *Lancet* 1994;343:1006-8.
3. Global Initiative for Asthma. Global strategy for asthma management and prevention. NHLBI/WHO Workshop Report. Bethesda (MD): National Institutes of Health; 2002. NIH publication no. 02-3659.

4. Lim S, Jatakanon A, Gordon D, Macdonald C, Chung KF, Barnes PJ. Comparison of high dose inhaled steroids, low dose inhaled steroids plus low dose theophylline, and low dose inhaled steroids alone in chronic asthma in general practice. *Thorax* 2000;55:837-41.
5. Ukena D, Harnest U, Sakalauskas R, Magyar P, Vetter N, Steffen H, et al. Comparison of addition of theophylline to inhaled steroid with doubling of the dose of inhaled steroid in asthma. *Eur Respir J* 1997;10:2754-60.
6. GOLD Global Initiative for Chronic Obstructive Lung Disease. Executive summary. Based on an April 1998 NHLBI/WHO Workshop, updated 2004. Available at: <http://www.goldcopd.com/>. Accessed January 17, 2006.
7. Kelloway JS, Wyatt RA, Adlis SA. Comparison of patients' compliance with prescribed oral and inhaled asthma medications. *Arch Intern Med* 1994;154:1349-52.
8. Nicholson CD, Shahid M. Inhibitors of cyclic nucleotide phosphodiesterase isoenzymes—their potential utility in the therapy of asthma. *Pulm Pharmacol* 1994;7:1-17.
9. Yasui K, Agematsu K, Shinozaki K, Hokibara S, Nagumo H, Nakazawa T, et al. Theophylline induces neutrophil apoptosis through adenosine A2A receptor antagonism. *J Leukoc Biol* 2000;67:529-35.
10. Ito K, Lim S, Caramori G, Cosio B, Chung KF, Adcock IM, et al. A molecular mechanism of action of theophylline: induction of histone deacetylase activity to decrease inflammatory gene expression. *Proc Natl Acad Sci U S A* 2002;99:8921-6.
11. Torphy TJ. Phosphodiesterase isozymes: molecular targets for novel antiasthma agents. *Am J Respir Crit Care Med* 1998;157:351-70.
12. Houslay MD. PDE4 cAMP-specific phosphodiesterases. *Prog Nucleic Acid Res Mol Biol* 2001;69:249-315.
13. Schudt C, Tenor H, Hatzelmann A. PDE isoenzymes as targets for antiasthma drugs. *Eur Respir J* 1995;8:1179-83.
14. Uckert S, Kuthe A, Stief CG, Jonas U. Phosphodiesterase isoenzymes as pharmacological targets in the treatment of male erectile dysfunction. *World J Urol* 2001;19:14-22.
15. Lee AJ, Chiao TB, Tsang MP. Sildenafil for pulmonary hypertension. *Ann Pharmacother* 2005;39:869-84.
16. Shapiro S. Proteinases in chronic obstructive pulmonary disease. *Transactions* 2002;30:98-102.
17. Hatzelmann A, Tenor H, Schudt C. Differential effects of non-selective and selective phosphodiesterase inhibitors on human eosinophil functions. *Br J Pharmacol* 1995;114:821-31.
18. Ariga M, Neitzert B, Nakae S, Mottin G, Bertrand C, Pruniaux MP, et al. Nonredundant function of phosphodiesterases 4D and 4B in neutrophil recruitment to the site of inflammation. *J Immunol* 2004;173:7531-8.
19. Rennard SI, Schacter N, Strek M, Rickard K, Amit O. Results of a 6-month, placebo-controlled study of a potent, selective inhibitor of phosphodiesterase 4. *Chest* 2006;129:565-6.
20. Barnette MS, Christensen SB, Essayan DM, Grous M, Prabhakar U, Rush JA, et al. SB 207499 (Arlotto), a potent and selective second-generation phosphodiesterase 4 inhibitor: in vitro anti-inflammatory actions. *J Pharmacol Exp Ther* 1998;284:420-6.
21. Gienbycz MA, Corrigan CJ, Seybold J, Newton R, Barnes PJ. Identification of cyclic AMP phosphodiesterases 3, 4 and 7 in human CD4+ and CD8+ T-lymphocytes: role in regulating proliferation and the biosynthesis of interleukin-2. *Br J Pharmacol* 1996;118:1945-58.
22. Au BT, Teixeira MM, Collins PD, Williams TJ. Effect of PDE4 inhibitors on zymosan-induced IL-8 release from human neutrophils: synergism with prostanooids and salbutamol. *Br J Pharmacol* 1998;123:1260-6.
23. Cortijo J, Villagrasa V, Navarrete C, Sanz C, Berto L, Michel A, et al. Effects of SCA40 on human isolated bronchus and human polymorphonuclear leukocytes: comparison with rolipram, SKF94120 and levcromakalim. *Br J Pharmacol* 1996;119:99-106.
24. Spoelstra FM, Berends C, Dijkhuizen B, de Monchy JG, Kauffman HF. Effect of theophylline on CD11b and L-selectin expression and density of eosinophils and neutrophils in vitro. *Eur Respir J* 1998;12:585-91.
25. Jones NA, Boswell-Smith V, Lever R, Page CP. The effect of selective phosphodiesterase isoenzyme inhibition on neutrophil function in vitro. *Pulm Pharmacol Ther* 2005;18:93-101.
26. Tenor H, Hatzelmann A, Church MK, Schudt C, Shute JK. Effects of theophylline and rolipram on leukotriene C4 (LTC4) synthesis and chemotaxis of human eosinophils from normal and atopic subjects. *Br J Pharmacol* 1996;118:1727-35.
27. Seldon PM, Barnes PJ, Meja K, Gienbycz MA. Suppression of lipopolysaccharide-induced tumor necrosis factor-alpha generation from human peripheral blood monocytes by inhibitors of phosphodiesterase 4: interaction with stimulants of adenyl cyclase. *Mol Pharmacol* 1995;48:747-57.
28. Siegmund B, Eigler A, Moeller J, Greten TF, Hartmann G, Endres S. Suppression of tumor necrosis factor-alpha production by interleukin-10 is enhanced by cAMP-elevating agents. *Eur J Pharmacol* 1997;321:231-9.
29. 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. *J Pharmacol Exp Ther* 2002;300:559-66.
30. 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. *Am J Respir Cell Mol Biol* 1999;20:292-302.
31. 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.
32. Blease K, Burke-Gaffney A, Hellewell PG. Modulation of cell adhesion molecule expression and function on human lung microvascular endothelial cells by inhibition of phosphodiesterases 3 and 4. *Br J Pharmacol* 1998;124:229-37.
33. Yoshimura T, Nagao T, Nakao T, Watanabe S, Usami E, Kobayashi J, et al. Modulation of Th1- and Th2-like cytokine production from mitogen-stimulated human peripheral blood mononuclear cells by phosphodiesterase inhibitors. *Gen Pharmacol* 1998;30:175-80.
34. Essayan DM, Kagey-Sobotka A, Lichtenstein LM, Huang SK. Differential regulation of human antigen-specific Th1 and Th2 lymphocyte responses by isozyme selective cyclic nucleotide phosphodiesterase inhibitors. *J Pharmacol Exp Ther* 1997;282:505-12.
35. Spina D, Harrison S, Page CP. Regulation by phosphodiesterase isoenzymes of non-adrenergic non-cholinergic contraction in guinea-pig isolated main bronchus. *Br J Pharmacol* 1995;116:2334-40.
36. Muller T, Engels P, Fozard JR. Subtypes of the type 4 cAMP phosphodiesterases: structure, regulation and selective inhibition. *Trends Pharmacol Sci* 1996;17:294-8.
37. Kwak HJ, Song JS, Heo JY, Yang SD, Nam JY, Cheon HG. Roflumilast inhibits lipopolysaccharide-induced inflammatory mediators via suppression of NF- κ B, P38 Map kinase and JNK activation. *J Pharmacol Exp Ther* 2005;30:98-102.
38. Barber R, Baillie GS, Bergmann R, Shepherd MC, Sepper R, Houslay MD, et al. Differential expression of PDE4 cAMP phosphodiesterase isoforms in inflammatory cells of smokers with COPD, smokers without COPD, and non-smokers. *Am J Physiol Lung Cell Mol Physiol* 2004;287:L332-43.
39. Jones NA, Leport M, Holand T, Vos T, Morgan M, Fink M, et al. Phosphodiesterase (PDE) 7 in inflammatory cells from patients with asthma and COPD. *Pulm Pharmacol Ther*. In press 2006. doi:10.1016/j.pupt.2005.11.010.
40. Tang H-F, Chen J-Q, Xie Q-M, Zheng X-Y, Zhu Y-L, Adcock I, et al. The role of PDE4 in pulmonary inflammation and goblet cell hyperplasia in allergic rats. *Biochim Biophys Acta* 2006. doi:10.1016/j.bbdis.2005.12.009.
41. Robichaud A, Stamatou PB, Jin SL, Lachance N, Macdonald D, Laliberte F, et al. Deletion of phosphodiesterase 4D in mice shortens alpha(2)-adrenoceptor-mediated anaesthesia, a behavioural correlate of emesis. *J Clin Invest* 2002;110:1045-52.
42. Lamontagne S, Meadows E, Luk P, Normandin D, Muise E, Boulet L, et al. Localization of phosphodiesterase-4 isoforms in the medulla and nodose ganglion of the squirrel monkey. *Brain Res* 2001;920:84-96.
43. Jin SL, Conti M. Induction of the cyclic nucleotide phosphodiesterase PDE4B is essential for LPS-activated TNF-alpha responses. *Proc Natl Acad Sci U S A* 2002;99:7628-33.
44. Gienbycz MA. Cilomilast: a second generation phosphodiesterase 4 inhibitor for asthma and chronic obstructive pulmonary disease. *Expert Opin Investig Drugs* 2001;10:1361-79.

45. Souness JE, Rao S. Proposal for pharmacologically distinct conformers of PDE4 cyclic AMP phosphodiesterases. *Cell Signal* 1997;9:227-36.
46. Bateman ED, Holmes M, Muir JF, Andrae K, Witte S, Bredenbroeker D. Safety profile of roflumilast, a novel, selective phosphodiesterase 4 inhibitor, in patients with moderate to severe COPD [abstract]. *Am J Respir Crit Care Med* 2004;169:A596.
47. Inflazyme pharmaceuticals. HT0712, a selective PDE4 inhibitor. Available at: www.inflazyme.com/corporate_profile. Accessed 2005.
48. Rabe KF, Bateman ED, ÓDonnell D, Witte S, Bethke TD. Roflumilast—an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomized controlled trial. *Lancet* 2005;366:563-71.
49. Draheim R, Egerland U, Rundfeldt C. Anti-inflammatory potential of the selective phosphodiesterase 4 inhibitor N-(3,5-Dichloro-pyrid-4-yl)-[1-(4-fluorobenzyl)-5-hydroxy-indole-3-yl]-glyoxylic acid amide (AWD 12-281), in human cell preparations. *J Pharmacol Exp Ther* 2004;308:555-63.
50. Trifilieff A, Wyss D, Walker C, Mazzoni L, Hersperger R. Pharmacological profile of a novel phosphodiesterase 4 inhibitor, 4-(8-benzo[1,2,5]oxadiazol-5-yl-[1,7]naphthyridin-6-yl)-benzoic acid (NVP-ABE171), a 1,7-naphthyridine derivative, with anti-inflammatory activities. *J Pharmacol Exp Ther* 2002;301:241-8.
51. Gale DD, Landells LJ, Spina D, Miller AJ, Smith K, Nichols T, et al. Pharmacokinetic and pharmacodynamic profile following oral administration of the phosphodiesterase (PDE)4 inhibitor V11294A in healthy volunteers. *Br J Clin Pharmacol* 2002;54:478-84.
52. Vakkalanka SKVS, Balasubramaniam LA, Gharat LA, Joshi VD, Husain N, Rao J, et al. The pharmacological and safety profile of a novel selective phosphodiesterase-4 (PDE4) inhibitor:GRC-3886. *Eur Respir J* 2004;24:1391.
53. Grootendorst DC, Gauw SA, Sterk PJ, Bethke TD, Hespers JJ, Hiemstra PS, et al. Treatment with PDE4 inhibitor roflumilast reduces sputum neutrophil and eosinophil numbers in patients with COPD [abstract]. *Proc Am Thor Soc* 2005;2:A543.
54. Engelstaetter R, Wingertzahn M, Schmid-Wirlitsch C, Leichtl S, Bredenbroeker D, Wurst W. Roflumilast, an oral once-daily Phosphodiesterase 4 (PDE4) Inhibitor does not exhibit bronchodilatory activity [abstract]. *Ann Allergy Asthma Immunol* 2005;94:169.
55. Martorana PA, Beume R, Lucattelli M, Wollin L, Lungarella G. Roflumilast fully prevents emphysema in mice chronically exposed to cigarette smoke. *Am J Respir Crit Care Med* 2005;172:848-53.
56. Van Schalkwyk E, Strydom K, Williams Z, Venter L, Leicht S, Schmid-Wirlitsch C, et al. Roflumilast, an oral, once-daily phosphodiesterase 4 inhibitor, attenuates allergen-induced asthmatic reactions. *J Allergy Clin Immunol* 2005;116:292-8.
57. Leichtl S, Syed J, Bredenbroeker D. Efficacy of once-daily roflumilast, a new orally active, selective phosphodiesterase 4 inhibitor, in chronic obstructive pulmonary disease [abstract]. *Am J Respir Crit Care Med* 2002;165:A229.
58. Bateman ED, Izquierdo JL, Vetter N, Schmid-Wirlitsch C, Bredenbroeker D. Roflumilast, a selective phosphodiesterase 4 inhibitor, shows efficacy and safety in the long-term treatment of asthma [abstract]. *Eur Respir J* 2003;22:A1393.
59. Aubier M, Nagy GB, Sauer R, Schmid-Wirlitsch C, Albrecht A, Bredenbroeker D. The novel selective PDE4 inhibitor roflumilast: early onset of efficacy in asthma [abstract]. *Eur Respir J* 2003;22:A1392.
60. Böszörményi-Nagy G, Pieters WR, Steffen H, Timar M, Vinkler I, Teichmann P, et al. The effect of roflumilast treatment and subsequent withdrawal in patients with COPD [abstract]. *Proc Am Thor Soc* 2005;2:A544.
61. Grootendorst DC, Gauw SA, Baan R, Kelly J, Murdoch RD, Sterk PJ, et al. Does a single dose of the phosphodiesterase 4 inhibitor, cilomilast (15 mg), induce bronchodilation in patients with chronic obstructive pulmonary disease? *Pulm Pharmacol Ther* 2003;16:115-20.
62. Bousquet J, Aubier M, Sastre J, Izquierdo JL, Adler LM, Hofbauer P, et al. Comparison of roflumilast, an oral anti-inflammatory, with beclomethasone dipropionate in the treatment of persistent asthma. *Allergy* 2006;61:72-8.
63. Bennett JA, Thompson Coon I, Pavord P, Wilding PJ, Tattersfield AE. The airway effects of stopping regular oral theophylline in patients with asthma. *Br J Clin Pharmacol* 1998;45:402-4.
64. Mecklenburg L, Heuser A, Juengling T, Kohler M, Foell R, Ockert D, et al. Mesenteritis precedes vasculitis in the rat mesentery after subacute administration of a phosphodiesterase type 4 inhibitor. *Toxicol Lett* 2005;163:54-64.
65. Losco PE, Evans EW, Barat SA, Blackshear PE, Reyderman L, Fine JS, et al. The toxicity of SCH 351591, a novel phosphodiesterase 4 inhibitor, in cynomolgus monkeys. *Toxicol Pathol* 2004;32:295-308.
66. Ariflo 15 mg. Available at: http://www.fda.gov/ohrms/dockets/ac/03/slides/3976S1_01_Glaxo-Ariflo_files/frame.htm#slide0648.htm. Accessed January 17, 2006.

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