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# COMMENTARY

# Can the anti-inflammatory potential of PDE4 inhibitors be realized: guarded optimism or wishful thinking?

MA Giembycz

*Department of Pharmacology & Therapeutics, Institute of Infection, Immunity and Inflammation, Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada*

PDE4 inhibitors have been in development as a novel anti-inflammatory therapy since the 1980s with asthma and chronic obstructive pulmonary disease (COPD) being primary indications. Despite initial optimism, none have yet reached the market. In most cases, the development of PDE4 inhibitors of various structural classes, including cilomilast, filaminast, lirimilast, piclamilast, tofimilast, AWD-12-281 (*aka* GSK 842470), CDP840, CI-1018, D-4418, IC485, L-826,141, SCH 351391 and V11294A has been discontinued due to lack of efficacy. A primary problem is the low therapeutic ratio of these compounds, which severely limits the dose that can be given. Indeed, for many of these compounds it is likely that the maximum tolerated dose is either sub-therapeutic or at the very bottom of the efficacy dose-response curve. Therefore, the challenge is to overcome this limitation. It is, therefore, encouraging that many 'new(er)' PDE4 inhibitors in development are reported to have an improved therapeutic window including tetomilast, oglemilast, apremilast, ONO 6126, IPL-512602 and IPL-455903 (*aka* HT-0712), although the basis for their superior tolerability has not been disclosed. In addition, other approaches are possible that may allow the anti-inflammatory activity of PDE inhibitors to be realized. Accordingly, this *Commentary* endorses the view of Spina (2008), published in the current issue of the *British Journal of Pharmacology*, that the therapeutic utility of PDE4 inhibitors to suppress inflammation still remains a viable concept.
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**Abbreviation:** COPD, chronic obstructive pulmonary disease

Glucocorticoids are the most effective anti-inflammatory agents currently available. However, there are many inflammatory diseases that are profoundly insensitive to glucocorticoids. Moreover, even in disorders in which glucocorticoids provide a mainstay therapy, there are individuals whose disease is not well controlled irrespective of dose or route of administration. The need to discover an alternative anti-inflammatory therapy of comparable efficacy but with a mechanism of action that is distinct from glucocorticoids is clear and led to the identification, in the late 1980s, of PDE4 as a viable target amenable to therapeutic intervention with small molecule inhibitors (Torphy and Undem, 1991). At that time, the chronic airways inflammation seen in asthma was considered a primary indication for PDE4 inhibitors. However, the enormous excitement generated by this potentially new class of anti-inflammatory drugs resulted, very rapidly, in an extension of the concept to include a myriad of other inflammatory and non-inflammatory disorders in which an elevation in cAMP is predicted to be beneficial. Twenty years later, PDE4 inhibitors still have not reached the market. Despite the many clinical trials and huge financial commitment by the pharmaceutical industry, most development candidates have been discontinued because of lack of efficacy and/or dose-limiting adverse events, with nausea, diarrhoea, abdominal pain, vomiting and dyspepsia being the most common. Indeed, a recent casualty is Pfizer's PDE4 inhibitor UK-500,001, the development of which for asthma and COPD was terminated due to lack of efficacy (www.apmhealtheurope.com/search_as.php?mots=UK-500%2C001&searchScope=1&searchType=0). Although phase III trials of PDE4 inhibitors continue, with oglemilast and tetomilast raising considerable interest, the lack of 'buzz' in the media so common in the 1990s tempts speculation that the development of many of these newer compounds also may be in difficulty.

Correspondence: Dr MA Giembycz, Department of Pharmacology and Therapeutics, Institute of Infection, Immunity and Inflammation, Faculty of Medicine, University of Calgary, 3330 Hospital Drive NW, Calgary, Alberta, Canada T2N 4N1.
E-mail: giembycz@ucalgary.ca
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In this issue of the *British Journal of Pharmacology*, Spina (2008) reviews the current status of PDE4 inhibitors for the treatment of asthma and COPD. Although the author's conclusion is one of guarded optimism, it seems clear that the method of inhibiting PDE4 needs to be refined if the therapeutic ratio of such compounds is to be improved. Alternatively, the development of more or less selective compounds as well as novel therapies in which a PDE4 inhibitor is one component of a combination of drugs could also provide an effective means of realizing clinical efficacy.

From the perspective of patient compliance, orally active PDE4 inhibitors, which exhibit efficacy with an acceptable therapeutic ratio, have always been a preferred development option. However, this objective has proved difficult to achieve primarily because adverse effects are evoked through the inhibition of PDE4 in non-target tissues at similar doses. Therefore, logic dictates that the therapeutic ratio of PDE4 inhibitors should be improved if systemic exposure is minimized. One means to achieve this end is to administer the drug of choice as a slow-release formulation such that the peak concentration achieved in the plasma is lowered, relative to overall systemic exposure. This approach has been successfully adopted for pentoxifylline, a non-selective PDE inhibitor, used in the treatment of peripheral vascular disease, cerebrovascular disease and a number of other conditions in which the regional microcirculation is compromised (Ward and Clissold, 1987). Theoretically, systemic exposure should also be reduced by directly applying PDE4 inhibitors to the airways as an inhaled formulation. However, this mode of delivery has not been effective. Indeed, AWD-12-281 and tofimilast were discontinued due to the lack of efficacy at, one must assume, their maximal tolerated doses (see http://health.apmnews.com/story.php?mots=tofimilast&rubrique=&profil=&country=&numero=6764&ctx=7ac9d516df281a9852a5e3807c52e359). It is not clear if these two compounds, given by inhalation, have sufficiently reduced emetic liability.

Perhaps the most enticing prospect is the development of a 'soft' PDE4 inhibitor. A 'soft' drug is biologically active having appreciable efficacy and stability at the site of application but is rapidly inactivated upon systemic exposure (Bodor and Buchwald, 2000). An example of such a drug for asthma is Nycomed's (Zurich, Switzerland) novel inhaled glucocorticoid, ciclesonide, which has unique pharmacokinetics. This unusual property results in the retention of ciclesonide in the lung with very limited systemic exposure due to low oral bioavailability ($\sim$1%) and considerable binding ($\sim$99%) of free drug to plasma proteins. Characteristics similar to these in a PDE4 inhibitor could markedly increase clinical efficacy and lower emetic potential. A further evolution could be the development of a long-acting 'soft' PDE4 inhibitor, which would facilitate compliance especially in subjects with COPD in whom treatment would necessarily be long term. In this context, long-acting PDE4 inhibitors (for example, RPL554 and RPL565) have been reported with biological activity persisting for many hours (Boswell-Smith *et al.*, 2006).

A clinically unexplored means to improve efficacy and therapeutic ratio may be provided by compounds with broader PDE selectivity (Giembycz, 2005, 2007). Spina's review highlights the fact that multiple PDE families are expressed in all structural and pro-inflammatory cells and that the collective targeting of these isoenzymes with hybrid inhibitors could provide superior anti-inflammatory activity when compared with a PDE4 inhibitor alone. Certainly, there is persuasive *in vitro* evidence that the selective inhibition of PDE3 or PDE7 in human T lymphocytes, monocytes and alveolar macrophages can enhance the inhibitory effect of a PDE4 inhibitor (Giembycz, 2005, 2007). The recent appreciation that PDE1 plays a major regulatory role in mitogenesis of smooth muscle cells tempts speculation that a dual PDE1/PDE4 could also display improved activity by arresting the hypertrophy and hyperplasia of airways smooth muscle cells, which is a consistent feature of asthma and COPD (Giembycz, 2007). Finally, some patients with COPD have coexisting pulmonary hypertension due to hypoxic pulmonary vasoconstriction. Clinically, PDE5 inhibitors are effective in reducing pulmonary vascular resistance and also suppress the proliferation of myocytes derived from human pulmonary artery. In these individuals, a case can be made to develop compounds with PDE4 and PDE5 inhibitory activity (Giembycz, 2005, 2007).

A logical extension to the aforementioned discussion on hybrid inhibitors is to consider whether non-selective compounds would have efficacy in combating chronic airways inflammation. Theophylline is known to exert anti-inflammatory activity in human participants with asthma when given at sub-bronchodilator doses, where the plasma concentration is between 5 and 10 $\mu g\,mL^{-1}$. Although this beneficial effect is often attributed to mechanisms unrelated to PDE inhibition, this interpretation is unnecessary. Indeed, theophylline even at a concentration of 5 $\mu g\,mL^{-1}$ (27 $\mu M$), and taking into account plasma protein binding, will inhibit, albeit modestly, PDEs1–5 by up to $\sim$20% depending on the isoenzyme. Thus, in addition to any beneficial effects produced by the inhibition of each PDE in isolation (see above), the probability for functional synergy when multiple PDEs are inhibited concurrently in the same cell types cannot be overstated (Giembycz, 2005 and above). Indeed, it is for this reason that PDE inhibition probably accounts for the anti-inflammatory mechanism of action of theophylline rather than some exotic activity peculiar to this compound. Accordingly, a prediction is that second generation non-selective PDE inhibitors could exhibit superior clinical efficacy over theophylline and compounds that selectively target PDE4. Moreover, because the mechanism of action relies on a modest inhibition of multiple PDEs, the potential for emesis and related gastrointestinal side effects, which are PDE4-mediated, should be minimized. Clearly, the design of such compounds should avoid the xanthine nucleus as a starting template to eliminate possible activity at adenosine receptors, which mediate many of the adverse cardiovascular and CNS effects of theophylline.

Another clinically unexplored approach to enhance anti-inflammatory activity is through combination therapies. It is entirely feasible that a PDE4 inhibitor may enhance the anti-inflammatory activity of an inhaled corticosteroid beyond that achievable by the steroid alone, in much the same way

as long-acting $\beta_2$-adrenoceptor agonists (Giembycz *et al.*, 2008). Indeed, in subjects with moderate asthma, low-dose inhaled budesonide with theophylline (mean plasma concentration = 8.7 $\mu g\,mL^{-1}$) and high-dose inhaled budesonide as a monotherapy are reported to produce similar clinical benefits in lung function, severity of disease and variability in peak expiratory flow rate, which is a correlate of airways hyper-responsiveness (Evans *et al.*, 1997). This general finding has been independently confirmed in several other trials in which the interaction of corticostertoids and theophylline in asthma control has been studied (Ukena *et al.*, 1997; Lim *et al.*, 2000). Thus, such an approach could be advantageous in asthmatic subjects not well controlled on an inhaled corticosteroid alone and in smoking asthmatic individuals and subjects with COPD who are relatively refractory to inhaled corticosteroids. Adding a long-acting $\beta_2$-adrenoceptor agonist to an inhaled corticosteroid and a PDE4 inhibitor in the form of a triple combination therapy could impart additional benefit by enhancing further the anti-inflammatory effect of the steroid as well as improving lung function though bronchodilatation.

Another approach is to seek increased selectivity for PDE4 inhibition. PDE4 isoenzymes are encoded by four genes (A–D), and it is believed that inhibition of enzymes encoded by *PDE4D* in non-target tissues promotes emesis. In contrast, selective inhibition of PDE4A and/or PDE4B in pro-inflammatory and immune cells is believed to evoke the therapeutically desired effects of these drugs (Jin *et al.*, 2007). As described by Spina (2008), a selective inhibitor of PDE4A and/or PDE4B should solve the emetic activity and associated adverse effects that have plagued compounds that inhibit all PDE4 gene products. Unfortunately, this objective has proved to be a major challenge to chemists, although some subtype-selective compounds have now been described. In particular, both Norvartis (Basel, Switzerland) and Pfizer (New York, USA) have reported compounds (NVP-ABE-171 and CP-671305, respectively) that are reasonably selective (30- to ~100-fold) for PDE4D. Although selective PDE4D inhibitors should be emetic and, therefore, not of therapeutic utility (see above), their discovery suggests that PDE4A- and PDE4B-selective compounds can also be synthesized. Another advantage of PDE4D-selective compounds is that they can be used in 'proof of concept' studies in non-human primates or other suitable animal models to delineate the functional role of PDE4D.

In conclusion, the review by Spina (2008) brings together the latest information on the status of PDE4 inhibitors for the treatment of asthma and COPD. It is clear that many compounds still in development may not reach the market as a monotherapy unless their emetic liability has been reduced. In this respect, data arising from the oglemilast and tetomilast clinical development programmes are awaited with much interest. However, even if the therapeutic ratio of these compounds has been improved, they still may not achieve the prominence in asthma and COPD treatment initially predicted. That said, opportunities for the development of more or less selective compounds or the use of a PDE4 inhibitor in combination with another drug (such as an inhaled corticosteroid) may provide new ways of harnessing the anti-inflammatory activity of PDE4 inhibitors to therapeutic advantage.

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