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REVIEW

Next Generation PDE4 Inhibitors that Selectively Target PDE4B/D Subtypes: A Narrative Review

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ABSTRACT

For decades, topical corticosteroids have been the mainstay of treatment for mild-to-moderate inflammatory skin diseases, even though only short-term use is approved for these agents and systemic inflammation is not addressed. Increased understanding of the immunopathogenesis of these conditions, especially for psoriasis and atopic dermatitis, has facilitated the development of antibody-based drugs that neutralize single key cytokines or their associated receptors, such as interleukin (IL)-17A/F, IL-23, and IL-17RA in psoriasis and IL-13 and IL-4Rα in atopic dermatitis. However, oral therapy is still preferred by many patients owing to the ease of use and needle-free administration. Phosphodiesterase 4 (PDE4) inhibitors have been approved for both oral and topical use for inflammatory skin diseases. In this review, we present a summary of an emerging class of selective PDE4B/D inhibitors under clinical development and compare the differences in selectivity of this new generation of PDE4 inhibitors with the less selective currently approved PDE4 inhibitors.

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Key Summary Points

Chronic inflammatory skin diseases are estimated to affect 20–25% of the world's population and the medical need persists for new safe and effective oral drugs for long-term treatment of chronic inflammatory skin diseases.

A new class of selective phosphodiesterase 4 subtype B and subtype D (PDE4B/D) inhibitors is emerging as four selective PDE4B/D inhibitor drug candidates (nerandomilast, zatolmilast, orismilast, and PF-07038124) are currently in late-stage clinical trials for diseases of the lung, brain, and skin.

Short isoforms of PDE4B/D—in particular PDE4B2 and PDE4D1/D2—are critical isoforms to block to achieve anti-inflammatory effects, and selective PDE4B/D inhibitors may drive higher efficacy than previously approved pan-phosphodiesterase 4 (pan-PDE4) inhibitors.

Next generation PDE4B/D inhibitors also have potential to affect comorbidities that are associated with chronic inflammatory skin diseases, including cardiometabolic disease.

INTRODUCTION

Chronic inflammatory skin diseases, including atopic dermatitis (AD), psoriasis, and hidradenitis suppurativa, are estimated to affect 20–25% of the world's population [1]. Beyond the burden of living with a life-long chronic skin disease, these patients also often have increased risk for comorbidities such as cardiovascular risk, and increased mortality [2]. Although biologic therapy for chronic inflammatory skin diseases has revolutionized the field of dermatology, from a patient perspective, safe and effective oral drugs are preferred by most [3]. Several orally available immunosuppressive drugs are available today for psoriasis and atopic dermatitis, including methotrexate, cyclosporine, and Janus kinase (JAK) inhibitors (e.g., JAK1 and TYK2 inhibitors such as upadacitinib, abrocitinib, and deucravacitinib); these medications, however, require monitoring for hepatotoxicity (methotrexate) [4, 5], nephrotoxicity (cyclosporine) [6], and/or serious adverse events such as infections, tuberculosis, thrombosis, cancer, and major adverse cardiovascular events (e.g., JAK1 and TYK2 inhibitors) [7]. While the development of apremilast, a pan-phosphodiesterase 4 (PDE4) inhibitor, offered patients with psoriasis a safer option than previous oral options, efficacy of this drug is limited. Accordingly, the medical need persists for new safe and effective oral drugs for long-term treatment of chronic inflammatory skin diseases. This review describes a new generation of oral PDE4B/D selective inhibitors under development and compares their PDE4 subtype profile with the approved PDE4 inhibitors currently used for treatment of psoriasis and atopic dermatitis. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

PDE4: AN IMMUNOMODULATORY TARGET LINKED TO CAMP

Cyclic adenosine monophosphate (cAMP) is a pivotal second messenger that regulates various cellular functions, including cell trafficking, release of inflammatory mediators, and immune cell proliferation. Drugs that elevate intracellular cAMP levels suppress immune functions of T cells, monocytes, macrophages, and neutrophils, by reducing the production of pro-inflammatory cytokines and by increasing the production of anti-inflammatory mediators (Fig. 1).

Intracellular levels of cAMP are tightly controlled on a subcellular level by

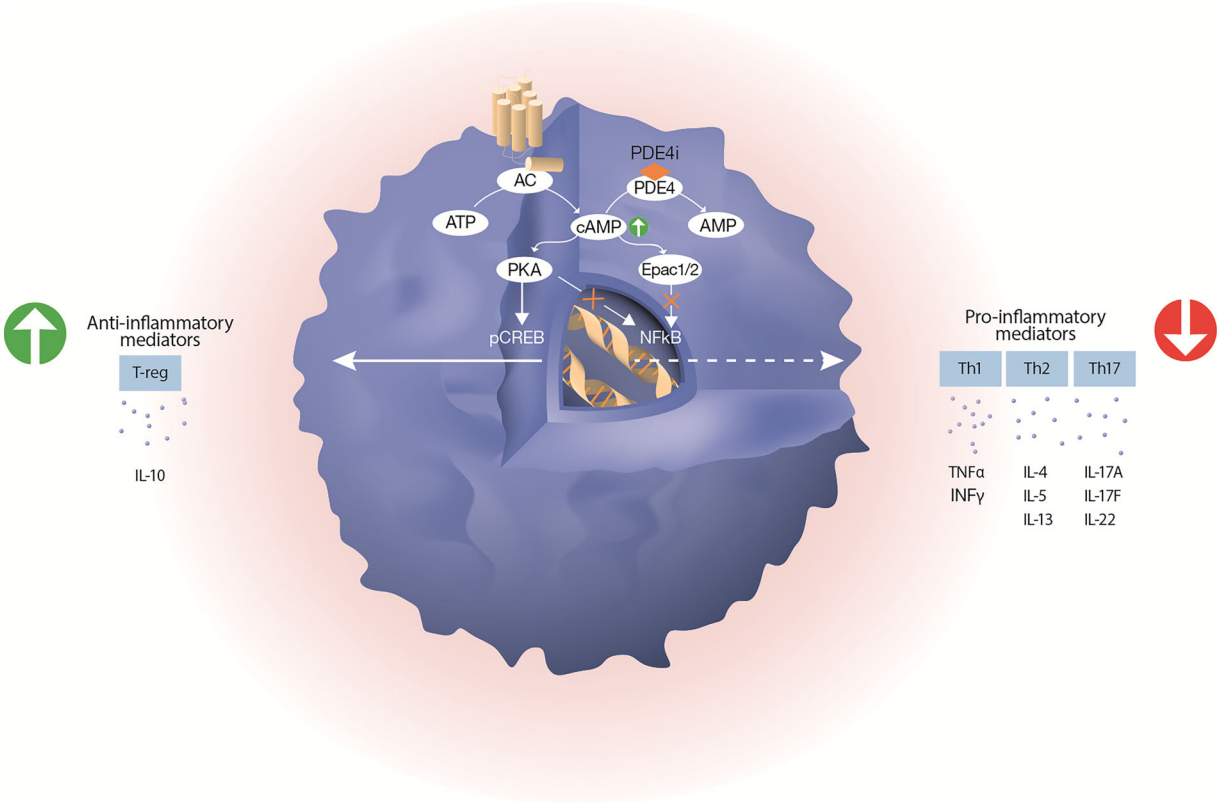

Fig. 1 Schematic illustration of how PDE4 inhibitors and cAMP are involved in resolving inflammation. Increased level of cAMP inhibits the production of pro-inflammatory cytokines through simultaneous inhibition of PKA-NFkB and Epac1/2-NFkB pathways; and promotes the production of anti-inflammatory mediators by activation of the PKA-CREB pathway. The intracellular level of cAMP is mainly controlled by the activity of adenylyl cyclase (AC) and phosphodiesterase 4 (PDE4). Upon stimulation, AC increases cAMP levels by converting ATP to cAMP. PDE4 controls the amplitude and duration of the cAMP signal by catalyzing the degradation of cAMP to AMP. Inhibition of PDE4 increases the intracellular levels of cAMP. Adenylyl cyclase (AC), phosphodiesterase 4 (PDE4), protein kinase A (PKA), exchange protein 1/2 activated by cAMP (Epac1/2), phosphorylated cAMP-responsive element binding protein (pCREB), nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), inhibitor of PDE4 (PDE4i) The figure was created with assistance from Erik Nylund, VisualizeThat AB

phosphodiesterases (PDEs), which are a superfamily of enzymes that inactivate cAMP and cyclic guanosine monophosphate (cGMP) [8]. PDEs are grouped into 11 distinct gene members (PDE1–PDE11), which each demonstrate different selectivity for cAMP and cGMP. PDE4 selectively degrades cAMP and accounts for most of the cAMP-hydrolyzing capacity within cells. Four subtypes exist (PDE4A/4B/4C/4D), which are expressed as approximately 20 PDE4 isoforms (splice variants) [9]. These isoforms are grouped into long isoforms (acting as homo- and heterodimers) and short/super-short isoforms (acting as monomers). Importantly, all PDE4 isoforms are unique proteins and can differ in their intracellular localization, three-dimensional structure, and cell type expression. Consequently, when profiling the affinity of PDE4 inhibitors against the various PDE4 isoforms, a PDE4 isoform fingerprint is displayed that dictates the effect of the inhibitor on different cell types and potential efficacy in different diseases.

The clinical importance of different PDE4 isoforms is not fully understood and only sparse information is available regarding the function

Table 1 Expression of PDE4 subtypes in primary human $CD4^+$ T cells and psoriatic PBMCs

	Gene expression in primary human $CD4^+$ T cells[a]	Protein expression in primary human $CD4^+$ T cells[a]	Gene expression in psoriatic PBMCs[b]
PDE4A	1	1	1
PDE4B	Eight-fold higher levels	Two-fold higher levels	Five-fold higher levels
PDE4C	Not detected	Not detected	Not detected
PDE4D	12-Fold higher levels	Three-fold higher levels	Two-fold higher levels

[a]Expression levels of each PDE4 subtype are shown relative to PDE4A
[b]Expression levels of each PDE4 subtype are shown relative to healthy donors

of the specific isoforms in human tissues. Inhibition of PDE4B and PDE4D subtypes is considered the main driver of the anti-inflammatory effects of PDE4 inhibitors, as these two subtypes are the only subtypes expressed in high levels in immune cells, e.g., human $CD4^+$ T cells and peripheral blood mononuclear cells (PBMCs). Conversely, PDE4C is largely absent in immune and blood cells (Table 1) [10–12].

Upon CD3/CD28 stimulation of primary human $CD4^+$ T cells, the PDE4B2 short isoform is transiently upregulated, whereas PDE4D1/D2 short isoforms are increasingly upregulated over time. By contrast, PDE4B long isoforms (PDE4B1/B3) are downregulated and PDE4A/PDE4D long forms (PDE4A4/A10 and PDED3/D4/D5/D7/D8/D9) are unaffected. The upregulation of short PDE4 splice variants was reported to account for the induction of PDE4 activity in stimulated $CD4^+$ T cells [10]. In human neutrophils and monocytes, the short PDE4B2 isoform is the predominant PDE4 isoform [13]. On the basis of these data, we propose that the short isoforms of PDE4B/D—in particular PDE4B2, PDE4D1, and PDE4D2—are critical isoforms to block to achieve anti-inflammatory effects (Fig. 2). Additional studies, however, are needed to fully establish the functional roles of the various PDE4 isoforms across different immune and tissue cell types.

Of note, PDE4D protein expression was reported as significantly increased in both the epidermis and dermis of patients with psoriasis and atopic dermatitis compared to healthy controls, whereas a more complex expression pattern was reported for the other subtypes [14]. Interestingly, recent evidence suggests that inhibition of PDE4D5 improves diabetes-associated cardiac dysfunction [15]. PDE4 inhibition has also been shown to reduce inflammation in human vascular endothelial cells [16]. These findings highlight an important opportunity for next generation PDE4B/D inhibitors to not only positively impact chronic inflammatory skin disease but to also affect comorbidities that are associated with these diseases including cardiovascular diseases.

APPROVED PDE4 INHIBITORS

Roflumilast was the first PDE4 inhibitor to be approved in 2010 for oral treatment of severe chronic obstructive pulmonary disease. This drug is rapidly metabolized to an active metabolite (roflumilast-N-oxide), which drives 90% of the efficacy and was reported to be a PDE4 inhibitor, without any particular selectivity for the various PDE4 isoforms (i.e., a pan-PDE4 inhibitor) [17]. Apremilast was the second PDE4 inhibitor to enter the market. Apremilast was initially approved for oral treatment of psoriasis in 2014, and later for psoriatic arthritis (2014) and Behcet's disease (2019). Apremilast is also reported to be a pan-PDE4 inhibitor without any PDE4 isoform selectivity [18].

Apremilast is widely used and it is relatively easy to manage this drug for both patients and prescribers, largely owing to its oral dosing and benign safety profile. However, at times, adverse reactions, in particular diarrhea, nausea, emesis,

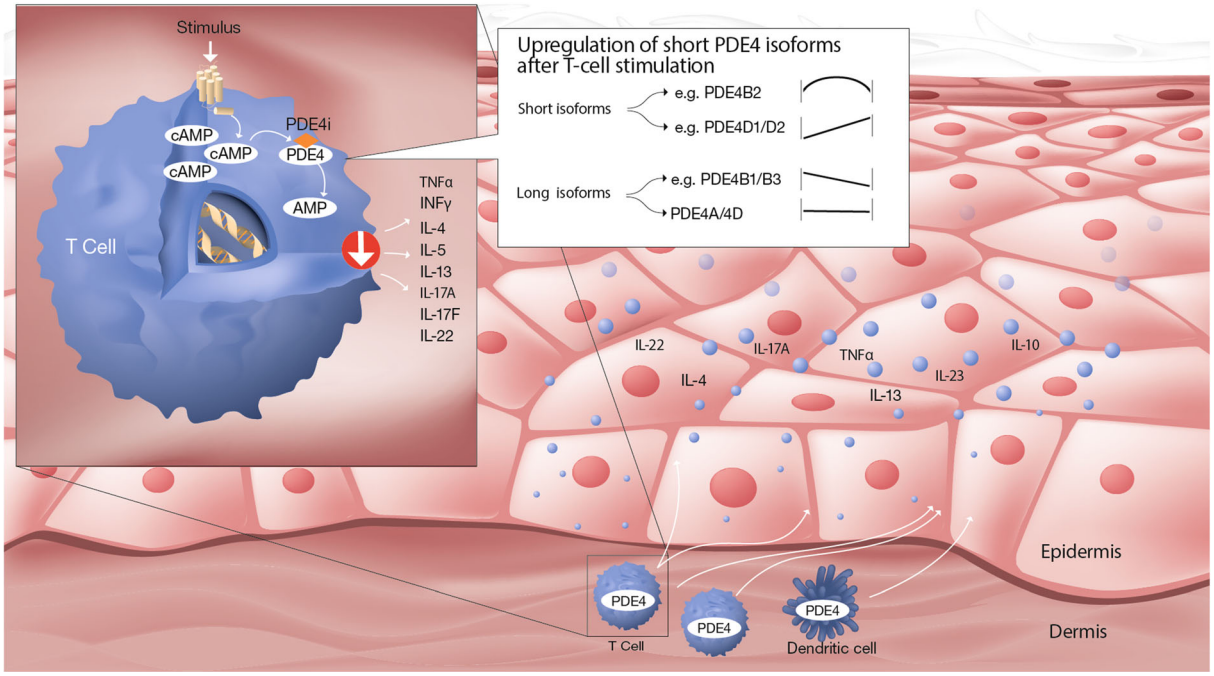

Fig. 2 Schematic illustration of the regulation of PDE4 isoforms in stimulated T cells and the importance of inhibiting short isoforms to prevent production of inflammatory cytokines in skin. The figure is based on PDE4 isoform data obtained using anti-CD3/CD28 stimulation of $CD4^+$ T cells [10]. The key findings were as follows: (i) The upregulation of short PDE4 splice variants was reported to account for the induction of PDE4 activity in stimulated $CD4^+$ T cells; (ii) PDE4B2 was transiently upregulated; (iii) PDE4D1/D2 were upregulated in a time-dependent manner; (iv) PDE4B1/B3 were downregulated over time; (v) Long PDE4A/4D isoforms were unchanged; and (vi) Short isoforms of PDE4A/PDE4C and long isoforms of PDE4C were not detected. Inhibition of PDE4B2 and PDE4D1/D2 leads to increased levels of cAMP and reduced levels of disease driving cytokines in the skin The figure was created with assistance from Erik Nylund, VisualizeThat AB

and headache, can be challenging. In addition, efficacy is limited [19, 20]. A recent link between cAMP and cystic fibrosis transmembrane conductance regulator (CFTR) has been reported which may, in part, explain the diarrhea [21]. CFTR is a chloride ion channel at the apical membrane of epithelial cells, including the intestine, and has a critical role in transepithelial chloride transport and intestinal fluid secretion/homeostasis. Upregulation of intracellular cAMP levels activate the CFTR channel, causing excessive fluid secretion and secretory diarrhea. To circumvent this potentially limiting adverse reaction, topically applied PDE4 inhibitors have been developed and approved. Topical roflumilast was approved in 2022 for treatment of psoriasis, and topical crisaborole and topical difamilast for treatment of atopic dermatitis in 2017 and 2022, respectively.

NEXT GENERATION PDE4 INHIBITORS BASED ON SELECTIVE INHIBITION OF THE PDE4B/D SUBTYPES

Following the approval of pan-PDE4 inhibitors, development of compounds that selectively inhibit PDE4B/D subtypes has received renewed attention. Indeed, four selective PDE4B/D inhibitor drug candidates are currently in late-stage clinical trials for diseases of the lung, brain, and skin (Table 2). Clinical data across several indications support the hypothesis that PDE4B/D inhibitors can achieve high clinical efficacy,

Table 2 Overview of approved PDE4 inhibitors and next generation PDE4B/D selective inhibitors in late-stage clinical development

Compound	Indication	Phase	Isoform data	Selectivity ratio[a]	PDE4 profile[b]
Roflumilast (oral and topical)	COPD	Approved	PDE4A1: 0.7 nM	PDE4 A/B = 1.8	High-potency, unselective PDE4 inhibitor
			PDE4A4: 0.9 nM	PDE4 A/D = 2.5	
			PDE4B1: 0.7 nM	PDE4 B/D = 1.4	
			PDE4B2: 0.2 nM	Unselective	
			[c]*PDE4C1: 3 nM*		
			[c]*PDE4C2: 4.3 nM*		
			PDE4D2: 0.3 nM		
			PDE4D3: 0.4 nM		
			PDE4D4: 0.2 nM		
			PDE4D5: 0.4 nM		
Apremilast (oral)	Psoriasis, psoriatic arthritis, and Behcet's disease	Approved	PDE4A1: 78 nM	PDE4 A/B = 1.0	Medium-potency, unselective PDE4 inhibitor
			PDE4A4: 42 nM	PDE4 A/D = 1.7	
			PDE4A10: 140 nM	PDE4 B/D = 1.8	
			PDE4B1: 61 nM	Unselective	
			PDE4B2: 97 nM		
			PDE4B3: 117 nM		
			[c]*PDE4C2: 244 nM*		
			PDE4D1: 44 nM		
			PDE4D2: 54 nM		
			PDE4D3: 54 nM		
			PDE4D4: 41 nM		
			PDE4D5: 61 nM		
			PDE4D7: 50 nM		

Table 2 continued

Compound	Indication	Phase	Isoform data	Selectivity ratio[a]	PDE4 profile[b]
Nerandomilast (oral)	Idiopathic pulmonary fibrosis and progressive fibrosing interstitial lung diseases	3	PDE4A: 248 nM	PDE4 A/B = 25	Potent, selective PDE4B inhibitor
			PDE4B2: 10 nM	PDE4 A/D = 2.7	
			[c]*PDE4C2: 8700 nM*	PDE4 D/B = 9.1	
			PDE4D2: 91 nM	Selective for B	
Zatolmilast (oral)	Fragile X syndrome	2b/3	PDE4D2: 127 nM	ND	Potent allosteric, PDE4D modulator
			[d]PDE4D7: 1018 nM		
			[c]PDE4D7: 8 nM		
			PDE4D3: 7 nM		
Orismilast (oral)	Psoriasis and atopic dermatitis	2b	PDE4A1: 16 nM	PDE4 A/B = 3.2	Potent, selective PDE4B/D inhibitor
			PDE4A4: 11 nM	PDE4 A/D = 7.5	
			PDE4A10: 52 nM	PDE4 B/D = 2.5	
			PDE4B1: 16 nM	Selective for B/D	
			PDE4B2: 6 nM		
			PDE4B3: 3 nM		
			[c]*PDE4C2: 104 nM*		
			PDE4D1: 9 nM		
			PDE4D2: 2 nM		
			PDE4D3: 2 nM		
			PDE4D4: 3 nM		
			PDE4D5: 2 nM		
			PDE4D7: 3 nM		

Table 2 continued

Compound	Indication	Phase	Isoform data	Selectivity ratio[a]	PDE4 profile[b]
Crisaborole [30] (topical)	Atopic dermatitis	Approved	PDE4A1: 52 nM	PDE4 B/D = 1.3	Medium-potency, selective PDE4A inhibitor
			PDE4B1: 61 nM	PDE4 D/A = 3.3	
			PDE4B2: 75 nM	PDE4 B/D = 1.4	
			[c]*PDE4C1: 340 nM*	Selective for A	
			PDE4D7: 170 nM		
PF-07038124 (topical)	Psoriasis and atopic dermatitis	2b	PDE4B2: 0.5 nM	ND	High-potency PDE4B2 inhibitor

ND not determined

[a]Unselective was defined as a potency ratio < three-fold when comparing the isoform with highest potency to the isoform with lowest potency. Selective was defined as a potency ratio ≥ three-fold when comparing the isoform with highest potency to the isoform with lowest potency. When more isoforms were reported within a PDE4 subtype, the average of the isoform data of a given subtype was used

[b]High potency was defined as a potency range of 0.1–0.9 nM. Potent was defined as a potency range of 1–10 nM. Medium potency was defined as a potency range of 11–1000 nM

[c]PDE4C isoform data are listed in italics and not considered when describing the PDE4 profile, since PDE4C isoforms were reported to be absent in immune and blood cells (see Table 1)

[d]This isoform was the basal dimer of PDE4D7

[e]This isoform was the activated dimer of PDE4D7

Apremilast data were generated head-to-head with orismilast [26]

opening these drugs for new clinical applications.

Nerandomilast is a selective PDE4B2 inhibitor, although rather limited PDE4 isoform data have been disclosed [22]. In addition to anti-inflammatory effects, nerandomilast also demonstrated an anti-fibrotic effect in preclinical models, as nerandomilast inhibited the transforming growth factor beta (TGFβ)-stimulated transformation of fibroblasts into myofibroblasts. In a phase 2 trial, nerandomilast prevented a decrease in lung function in patients with idiopathic pulmonary fibrosis over a period of 12 weeks [23]. Nerandomilast is currently undergoing phase 3 clinical testing in idiopathic pulmonary fibrosis and progressive fibrosing interstitial lung diseases.

Zatolmilast is a brain-penetrating allosteric modulator of PDE4D. The compound selectively and partially inhibits activated dimeric isoforms of PDE4D when compared to monomeric and basal forms [24]. In theory, modulation of PDE4D (rather than complete inhibition) is predicted to improve cognitive function by prolonging cAMP activity. In a phase 2 trial, zatolmilast met key secondary efficacy measures of cognition and daily function in patients with fragile X syndrome [25]. This compound is currently being studied in a phase 2b/3 trial in the same indication.

Orismilast is a PDE4B/D selective inhibitor that has been profiled against 13 PDE4 isoforms and shown to selectively inhibit PDE4B/D isoforms [26]. In addition, orismilast potently inhibits the secretion of several key disease-driving cytokines (e.g., tumor necrosis factor (TNF)α, IL-17A, and IL-13) in preclinical models. In the clinic, orismilast has shown promising efficacy data in a placebo-controlled, phase 2b study in patients with moderate-to-severe psoriasis [27]. Furthermore, orismilast has shown encouraging data in hidradenitis suppurativa [28] and is currently being studied in a phase 2b trial in patients with atopic dermatitis.

PF-07038124 is a potent PDE4B2 inhibitor designed to be applied to the skin, using a soft-drug approach, whereby the drug is rapidly inactivated when it reaches the systemic circulation. No additional PDE isoform data has been disclosed for PF-07038124. PF-07038124 is currently being studied for topical treatment of both psoriasis and atopic dermatitis [29].

CONCLUSION

A new class of selective PDE4B/D inhibitors is emerging. Based on clinical data across psoriasis, atopic dermatitis, idiopathic pulmonary fibrosis, and fragile X syndrome, the combination of potent yet selective mechanism of action offers new opportunities for clinical applications. Combined with the proven safety of the pan-PDE4 inhibitors, novel selective PDE4B/D inhibitors offer a potential new treatment approach for the long-term management of chronic inflammatory and fibrotic diseases.

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Declarations

Conflict of Interest. Andrew Blauvelt has served as a speaker (received honoraria) for AbbVie, Bristol-Myers Squibb, Eli Lilly and Company, Pfizer, Regeneron, and Sanofi, served as a scientific adviser (received honoraria) for AbbVie, Abcentra, Aclaris, Affibody, Aligos, Almirall, Alumis, Amgen, Anaptysbio, Apogee,

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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