



## Commentary

## Apremilast mechanism of action and application to psoriasis and psoriatic arthritis

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## ABSTRACT

Psoriasis and psoriatic arthritis are common clinical conditions that negatively impact health-related quality of life and are linked to serious medical comorbidities. Disease mechanisms involve local and systemic chronic inflammatory processes. Available biologic therapies specifically target single inflammatory mediators, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), in the context of a larger inflammatory signaling cascade. To interrupt this pathological cascade earlier in the response or further upstream, and return pro-inflammatory and anti-inflammatory signaling to a homeostatic balance, the use of a phosphodiesterase4 (PDE4) inhibitor has been explored. PDE4 is the major enzyme class responsible for the hydrolysis of cyclic adenosine monophosphate (cAMP), an intracellular second messenger that controls a network of pro-inflammatory and anti-inflammatory mediators. With PDE4 inhibition, and the resulting increases in cAMP levels in immune and non-immune cell types, expression of a network of pro-inflammatory and anti-inflammatory mediators can be modulated. Apremilast is an orally available targeted PDE4 inhibitor that modulates a wide array of inflammatory mediators involved in psoriasis and psoriatic arthritis, including decreases in the expression of inducible nitric oxide synthase, TNF- $\alpha$ , and interleukin (IL)-23 and increases IL-10. In phase II studies of subjects with psoriasis and psoriatic arthritis, apremilast reversed features of the inflammatory pathophysiology in skin and joints and significantly reduces clinical symptoms. The use of an oral targeted PDE4 inhibitor for chronic inflammatory diseases, like psoriasis and psoriatic arthritis, represents a novel treatment approach that does not target any single mediator, but rather focuses on restoring a balance of pro-inflammatory and anti-inflammatory signals.

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## 1. Introduction

Psoriasis is a chronic inflammatory disease predominantly affecting the skin and is estimated to occur in 2–3% of the population [1,2]. A subset of these psoriasis patients will also develop psoriatic arthritis, a seronegative spondyloarthropathy [3,4]. In psoriasis and psoriatic arthritis, a dysregulation of multiple pro-inflammatory and anti-inflammatory mediators occurs in dendritic cells, monocytes, macrophages, neutrophils, T cells, B cells, keratinocytes, chondrocytes, and synoviocytes

[5,6]. The cascade of aberrant immune signaling, triggered by stress, physical injury, drugs, or infection, is believed to underlie the clinical signs of inflammation, pain, and pruritus, as well as the histological signs such as keratinocyte hyperproliferation, scaling, and, in subsets of patients, pustular or guttate plaques and nail and joint involvement [5,7]. Because of the chronic nature of psoriasis and psoriatic arthritis, long-term treatment is often required [8]. Systemic therapies are typically recommended for patients with moderate psoriasis affecting 3–10% of the body surface area, and for severe psoriasis affecting more than 10% of the body surface area, or for patients who experience significant psoriasis-related impairments in quality of life [7–9]. Traditional systemic or disease-modifying antirheumatic drugs (DMARDs) include methotrexate and cyclosporine; however, these agents are associated with serious organ toxicity and adverse effects and require clinical monitoring throughout treatment [9]. Additionally, evidence for the efficacy of methotrexate in psoriatic arthritis is limited, although methotrexate is often used as a first-line therapy because of its oral route of administration and lower cost, compared with the newer, more effective biologic treatments [3]. These biologic therapies include inhibitors of tumor necrosis

**Abbreviations:** ACR20, 20% or greater improvement from baseline in American College of Rheumatology; cAMP, cyclic adenosine monophosphate; CREB, cAMP-response element binding protein; DMARDs, disease-modifying antirheumatic drugs; IC<sub>50</sub>, half maximal inhibitory concentration; IFN- $\alpha$ , interferon- $\alpha$ ; IL, interleukin; iNOS, inducible nitric oxide synthase; NF- $\kappa$ B, nuclear factor kappa B; PDE, phosphodiesterase; PDE4, phosphodiesterase 4; PKA, protein kinase A; Th1, type 1 helper T cell; Th17, type 17 helper T cell; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; VEGF, vascular endothelial growth factor.

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factor- $\alpha$  (TNF- $\alpha$ ), interleukin 12 and 23 (IL-12/IL-23), and antibodies that target B cells or T cells [7,8]. Although biologic therapies represent an advance in the treatment of chronic inflammatory diseases, their use is limited by treatment resistance (including both initial lack of efficacy and loss of effect), tolerability issues, parenteral administration, and barriers to patient access, such as high cost and specialist management [7,8]. Research efforts continue in the search for oral treatment options that are safe and effective in the treatment of psoriasis and psoriatic arthritis.

## 2. Pathophysiology of psoriasis and dermatologic inflammation

Acute inflammatory reactions typically occur in response to infection and are coupled with the release of local factors that prevent excessive trafficking of leukocytes, allowing for resolution of inflammation. Resolution of an acute inflammatory response within the local tissues and a re-establishment of immunological homeostasis are necessary for ongoing health [10]. Skin is an important site for antigen presentation, and epidermal Langerhans cells and dermal dendritic cells play pivotal roles in T cell-mediated immune responses to antigens encountered in skin. Regulatory feedback loops help to balance pro-inflammatory signaling pathways and anti-inflammatory signaling pathways, maintaining the homeostatic functioning of the skin immune system [11].

In psoriasis and psoriatic arthritis, subsets of dendritic cells are believed to be involved in the very earliest stages of disease pathophysiology because they are the antigen-presenting cells that initiate dysregulated immune responses to antigens [12,13]. Although not fully understood, plasmacytoid dendritic cells appear to circulate in the blood of individuals with psoriasis and become activated upon interaction with antimicrobial peptides that are complexed with host DNA [12]. Activated plasmacytoid dendritic cells then produce interferon- $\alpha$  (IFN- $\alpha$ ), which interacts with keratinocytes and myeloid dendritic cells to affect pro-inflammatory processes [12]. Activated dendritic cells also produce pro-inflammatory mediators, such as IL-12 and IL-23 [12]. In lesional skin from subjects with psoriasis, inflammatory myeloid dendritic cells express TNF-related apoptosis-inducing ligand (TRAIL), which is likely a direct mediator of keratinocyte inflammation [13]. The myeloid dendritic cell/T cell interaction is central to the evolution of psoriasis [12]. T cells respond to myeloid dendritic cell antigen presentation by proliferating and differentiating into type 1 helper T cells (Th1) and type 17 helper T cells (Th17), which secrete cytokines, including IL-2, IFN- $\gamma$ , TNF- $\alpha$ , IL-17, and IL-22 [12].

In line with propagation of immune cell activation, individuals with psoriasis and psoriatic arthritis exhibit increased levels of pro-inflammatory mediators in both the target tissues and the blood. Compared with normal skin biopsies, psoriatic skin lesions have a Th1 and Th17 cytokine profile, including IL-2, IFN- $\gamma$ , TNF- $\alpha$ , IL-17, and IL-22, without a significant component of type 2 cytokines (i.e. IL-4, IL-5, and IL-10) [14,15]. Furthermore, immunoreactivity for IL-12 and IL-23 is significantly enhanced in lesional psoriatic skin compared with non-lesional and normal skin ( $P < 0.001$  for both) [16]. Significantly increased mRNA expression of IL-17A ( $P = 0.0059$ ), IL-17C ( $P = 0.0096$ ), and IL-17F ( $P = 0.0036$ ) was observed in psoriatic skin compared with nonlesional skin [17]. Similarly, for subjects with psoriatic arthritis, IL-17A expression was found to be significantly higher ( $P < 0.01$ ) in synovial fluid of subjects with psoriatic arthritis (mean 4.5% [SD 0.9]) than in subjects with osteoarthritis (mean 1.14% [SD 0.9]) [18].

Pro-inflammatory mediators seen in psoriasis and psoriatic arthritis are released by a variety of cell types, including innate

immune cells, adaptive immune cells, and resident non-immune cells. Immunostaining of psoriatic lesional skin sections confirmed significantly higher expression of both subunits of IL-23 (p19 and p40) by keratinocytes in situ compared with keratinocytes in normal ( $P = 0.001$ ) and psoriatic nonlesional ( $P < 0.05$ ) skin [19]. CD11+ dendritic cells are a major cell type in psoriatic skin lesions. In diseased skin, these cells express two mediators of inflammation: inducible nitric oxide synthase (iNOS) and TNF- $\alpha$  in diseased skin [20]. Moreover, relatively high percentages of epidermal CD8 and CD4T cells isolated from psoriatic lesions are capable of producing IFN- $\gamma$ , TNF- $\alpha$ , and IL-2, whereas few T cells express IL-4 or IL-10 [21]. IL-17(+) mast cells and neutrophils are found at higher densities than IL-17(+) T cells in psoriatic lesions and frequently release IL-17 [22].

Such chronic inflammatory signaling is believed to lead to changes in resident cells of the skin and joints. In the skin, feedback loops involving keratinocytes, fibroblasts, and endothelial cells contribute to tissue reorganization, marked by endothelial-cell proliferation and deposition of extracellular matrix [12]. Total blood vessel and lymphatic vessel areas are increased in psoriatic skin lesions compared with non-involved skin, which accounts for lesion redness [23]. Angiogenic markers, such as vascular endothelial growth factor (VEGF)-A, placental growth factor, VEGFR2, and neuropilin-1, are also increased [23]. In one study, subjects with psoriatic arthritis had higher circulating concentrations of Dickkopf-1 and macrophage-colony stimulating factor (two soluble mediators of bone remodeling) than individuals with psoriasis or healthy controls; the macrophage-colony stimulating factor concentrations positively correlated with radiographic joint erosion, joint-space narrowing, and osteolysis scores [24].

## 3. Role of cAMP and PDE4 in regulating inflammation

One limitation of currently available biologic agents is that they do not reach inside the cell to target intracellular signaling pathways. Instead, such agents are antibodies or compounds that selectively bind with receptors or proteins on extracellular membranes or extracellular milieu (e.g. anti-TNF), altering activity of targeted cell types, cell-to-cell interactions, and immune signaling [5]. Biologic agents tend to specifically target a single pro-inflammatory marker and interrupt the inflammatory cascade downstream from pro-inflammatory changes in gene transcription. To interrupt the inflammatory cascade at an earlier point, researchers have begun to explore modulation of intracellular signaling that controls inflammatory-mediator gene expression. Intracellular signaling and responses to environmental factors by all types of cells throughout the body, including myeloid, lymphoid, and other inflammatory cells, are regulated by key "second messengers", such as cyclic adenosine monophosphate (cAMP).

Intracellular concentrations of cAMP levels represent a balance between the activities of the various adenylyl cyclases largely activated via G-protein coupled receptors and the phosphodiesterases (PDEs), of which 11 distinct families are expressed in a tissue-specific manner [25,26]. Eight PDE families are capable of hydrolyzing cAMP to AMP [27]. With four different PDE4 subtypes (A, B, C, and D) and more than 20 different isoforms defined so far, this large enzyme family manages a wide array of distinct cAMP signaling pathways that are specifically tailored to different types of cells [27]. Phosphodiesterase4 (PDE4) is one of the major cAMP-selective PDEs expressed in epithelial cells, such as those lining the airways [28]. Hematopoietic cells controlled by PDE4 include dendritic cells, T cells, macrophages, and monocytes [27,29–31]. Mesenchymal cells that express PDE4 include keratinocytes within the dermis, smooth muscle, vascular endothelium, and chondrocytes involved in the structure of the joint [27,32,33]. In the central

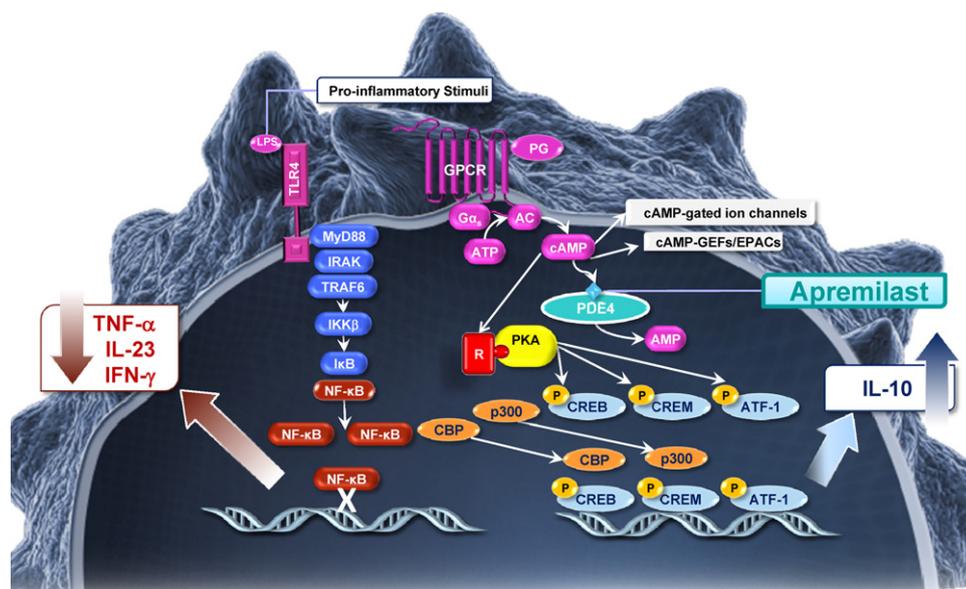
nervous system, neurons in the area postrema, which controls the emetic reflex, express PDE4 [34]. By decreasing intracellular cAMP, PDE4 promotes production of pro-inflammatory mediators and decreases production of anti-inflammatory mediators. Conversely, inhibition of PDE4 increases the intracellular concentration of cAMP and preferentially blocks pro-inflammatory cytokines, such as TNF- $\alpha$ , IFN- $\gamma$ , and IL-2 production from peripheral blood monocytes and T cells [35], and increases anti-inflammatory mediators, such as IL-10 [36]. In light of the central role of PDE4 in regulating inflammatory mediators [25,37], intense research interest has focused on compounds capable of modulating activity of this enzyme subfamily.

It has been known for some time that increases in cAMP levels within the cell result in activation of cAMP-dependent protein kinase A (PKA) [38]. More recently, the importance of local cAMP concentrations within microdomains inside the cell has also been recognized as an important aspect of this second messenger system [39]. The activation of PKA, in turn, activates certain transcription factors (e.g. cAMP-response element binding protein [CREB]) [40], but inhibits others (e.g. nuclear factor kappa B [NF- $\kappa$ B]). The cAMP-induced activation of the CREB family factors and the inhibition of NF- $\kappa$ B activation have been reported by several investigators. For example, in primary human T cells, rolipram, a pan PDE4 inhibitor, has been shown to inhibit NF- $\kappa$ B and nuclear factor of activated T cells transcriptional activity but also to enhance the cAMP-response element and AP-1 driven transcription [41,42]. In TNF-stimulated Jurkat T cells, forskolin (an adenylyl cyclase activator), or dibutyryl-cAMP (a PKA activator) inhibited

NF- $\kappa$ B driven transcription, but not I $\kappa$ B $\alpha$  degradation or NF- $\kappa$ B DNA binding activity [43]. Furthermore, dibutyryl-cAMP inhibited lipopolysaccharide-induced NF- $\kappa$ B activity, but not p65 nuclear translocation or I $\kappa$ B $\alpha$  degradation in THP-1 cells [44]. Finally, rolipram inhibited lipopolysaccharide-induced NF- $\kappa$ B luciferase activity in alcohol-exposed RAW264.7 mouse macrophages [45]. Thus, NF- $\kappa$ B luciferase activity has consistently been shown to be inhibited by these cAMP-elevating agents in several cell types through a mechanism of transcriptional inhibition but not the upstream signaling pathway. The mechanism by which PKA activation results in NF- $\kappa$ B inhibition has been shown to be either indirect, through competition for the transcriptional coactivator CREB binding protein (CBP or the homologous protein p300) [46], or through modification of the C-terminal transactivation domain of the NF- $\kappa$ B subunit p65 [43]. cAMP can also affect intracellular signaling via cyclic nucleotide-gated ion channels, or via the exchange protein activated by cAMP (Epac) [47]. Through its actions at the transcriptional level, cAMP helps maintain immune homeostasis by modulating the production of pro-inflammatory and anti-inflammatory mediators (Fig. 1).

#### 4. Apremilast in vitro pharmacology and activity in nonclinical models relevant to psoriasis

PDE4 inhibitors are a class of low molecular weight compounds that exhibit anti-inflammatory effects in several preclinical models [27,48] and clinically with various chronic inflammatory diseases, including psoriasis [49], psoriatic arthritis [50], atopic dermatitis



**Fig. 1.** Apremilast specifically targets PDE4 and modulates expression of a network of pro-inflammatory and anti-inflammatory mediators. The inflammatory process in psoriasis and arthritis results from an interplay between innate immune cells (dendritic cells, macrophages, and neutrophils), adaptive immune cells (T cells), and even non-immune cells (keratinocytes, synovial fibroblasts, and chondrocytes). The production of pro-inflammatory and anti-inflammatory mediators is modulated in these cell types through the enzyme phosphodiesterase 4 (PDE4). Pro-inflammatory signals such as those emanating from the toll-like receptor (TLR4) pathway in cells such as monocytes and dendritic cells result in activation of the transcription factor nuclear factor-kappa B (NF- $\kappa$ B) and the expression of pro-inflammatory mediators such as interleukin (IL)-23, tumor necrosis factor (TNF)- $\alpha$ , and interferon (IFN)- $\gamma$ . Simultaneously, signals emanating from G-protein coupled receptors (GPCRs) such as those binding prostaglandin (PG) act via the stimulatory G protein alpha subunit ( $G_{\alpha_s}$ ) to activate adenylyl cyclase (AC), resulting in production of cyclic adenosine monophosphate (cAMP). In white blood cells such as monocytes and dendritic cells, cAMP is degraded to AMP largely through hydrolysis by PDE4. PDE4 inhibition by Apremilast increases cAMP levels within the cells, which results in activation of protein kinase A (PKA), as well as cyclic nucleotide-gated ion channels, or the exchange protein activated by cAMP (Epac). PKA activation results in phosphorylation of the cAMP responsive element (CRE) binding family of transcription factors, including cAMP responsive element binding protein (CREB), cAMP responsive element modulator (CREM), and activating transcription factor 1 (ATF-1). In certain cell types such as monocytes, these factors bind to CRE sites within promoters of genes such as IL-10, resulting in increased gene expression. CRE-driven transcriptional activation recruits coactivators such as CREB binding protein (CBP) or the homologous protein p300, which have histone acetyl transferase activity. Recruitment of CBP and p300 away from NF- $\kappa$ B results in inhibition of NF- $\kappa$ B transcriptional activity, and a reduction in NF- $\kappa$ B dependent gene expression, thereby resulting in a decrease in IL-23, TNF- $\alpha$ , and IFN- $\gamma$  production. The decreased inflammatory response may lead to lower levels of infiltration by other immune cells, as well as reduced activation and proliferation of keratinocytes and synoviocytes. Together, this may lead to decreased epidermal thickening in psoriasis and decreased synovial damage in arthritis. Other Apremilast mechanisms of action, such as direct effects on keratinocytes and synoviocytes, may also occur (see Table 1).

[51], and inflammatory bowel disease [52]. Apremilast is a novel, orally available small molecule that specifically targets PDE4 [53]. Through this targeted inhibition, apremilast elevates intracellular cAMP levels, partially inhibiting the production of many pro-inflammatory mediators and increasing the production of some anti-inflammatory mediators, with stronger effects on innate immunity compared with adaptive immunity [54]. Characterization of its pharmacological effects using in vivo assays with lipopolysaccharide-stimulated human peripheral blood mononuclear cells and lipopolysaccharide-stimulated human whole blood showed that apremilast reduces PDE4 activity and decreases expression of the key pro-inflammatory mediator TNF- $\alpha$  [53]. Pharmacokinetic profiling of apremilast showed that, with oral or intravenous administration in female rats, it exhibits a low clearance rate, moderate volume of distribution, and 64% bioavailability following an oral dose [53]. Using PDE4 isolated from U937 cell preparations, apremilast exhibited a half maximal inhibitory concentration (IC<sub>50</sub>) of 74 nM using 1- $\mu$ M cAMP as substrate [55]. Lineweaver–Burke analysis using various concentrations of apremilast (0.03–5  $\mu$ M), and a range of substrate concentrations (0.625–10  $\mu$ M cAMP), indicated competitive binding [55]. Apremilast showed no marked selectivity among the individual PDE4 isotypes (A, B, C, and D). However, apremilast was more potent in reducing PDE4 activity than hydrolyzing enzymes from other PDE families [55]. The effects of apremilast on a range of pro-inflammatory responses in a variety of cell types also have been examined [55]. In lipopolysaccharide-stimulated peripheral blood mononuclear cells from healthy human donors, apremilast reduced the production of TNF- $\alpha$  (IC<sub>50</sub> = 0.11  $\mu$ M), IFN- $\gamma$  (IC<sub>50</sub> = 0.013  $\mu$ M), IL-12p70 (IC<sub>50</sub> = 0.12  $\mu$ M), and IL-23A, as well as the chemokines CXCL9 (MIG), CXCL10 (IP-10), and CCL4 (MIP1a) [55]. By contrast, apremilast was found to increase expression of IL-10 in lipopolysaccharide-stimulated peripheral blood mononuclear cells at 1  $\mu$ M,

while IL-6 was only significantly elevated at 10  $\mu$ M (well above the estimated maximum attainable plasma concentration of 1.5  $\mu$ M). Meanwhile, expression of IL-1 $\beta$  and IL-8 was unchanged under these conditions [55]. Moreover, apremilast partially inhibited TNF- $\alpha$  production by keratinocytes irradiated with 50 mJ cm<sup>-2</sup> of UVB light, but did not affect keratinocyte proliferation under these conditions. In a murine psoriasis model using human skin xenografted onto Beige-SCID mice and activated with psoriatic patient natural killer cells, oral apremilast led to a significant reduction in epidermal lesion thickness and proliferation, similar to cyclosporine, and psoriasiform histology was reduced in four of seven (57%) apremilast-treated mice compared with three of seven (42.9%) cyclosporine-treated mice [55]. TNF- $\alpha$  expression was down-regulated in four of the seven (57%) grafts treated with apremilast and in six of the seven (86%) grafts treated with cyclosporine. Therefore, while the overall effect of apremilast and cyclosporine on the skin pathology appeared to be of a similar magnitude, cyclosporine treatment resulted in a qualitatively greater decrease in TNF- $\alpha$  protein expression in the skin due to the only partial inhibition of TNF- $\alpha$  expression by apremilast. In this model, apremilast treatment resulted in a normalization of the skin histology, including a reduction in parakeratosis, hyperkeratosis, neutrophilia (Munro micro-abscess formation), lymphocytic infiltration, and epidermal thickening [55]. These data illustrate the effects of apremilast on several aspects of the psoriatic response, including inhibition of reduced inflammatory responses of toll-like receptor 4-mediated signaling in mononuclear cells, inhibition of neutrophils (both components of the innate immune system), reduced production of multiple pro-inflammatory cytokines and chemokines (including IL-23 and TNF- $\alpha$ ), enhancement of IL-10 production, and inhibition of keratinocyte responses. A summary of the effects of apremilast on various cell types related to psoriasis pathophysiology is presented in Table 1.

**Table 1**  
Apremilast effects on various cell types associated with pathophysiology of psoriasis and arthritis.

Cell type	Stimulation	Receptor type	Readout	IC <sub>50</sub> ( $\mu$ M) or % change <sup>a</sup>	Ref.
PBMC	LPS	TLR4	CXCL10 (IP-10)	0.0099	[54]
			IFN- $\gamma$	0.013	
			CXCL9 (MIG)	0.028	
			TNF- $\alpha$	0.11	
			IL-12p70	0.12	
			CCL3 (MIP-1 $\alpha$ )	0.44	
			CCL2 (MCP-1)	1.3	
			IL-10	73% increase at 1 $\mu$ M ( $P < 0.01$ )	
PMN	Zymosan	TLR2	CXCL8 (IL-8)	0.094	[54]
			CD18	0.39	
			CD11b	0.074	
			HUVEC adhesion	0.15	
			LTB4	0.0025	
T cells	Anti-CD3	TCR	IL-13	0.033	[63]
			IFN- $\gamma$	0.15	
			TNF- $\alpha$	0.18	
			CXCL10 (IP-10)	0.28	
			IL-2	0.33	
			CCL3 (MIP-1 $\alpha$ )	0.43	
			CCL4 (MIP-1 $\beta$ )	0.56	
			IL-4	0.78	
NK cells	IL-2 + IgG	Cytokine + Fc $\gamma$ R	TNF- $\alpha$	41% inhibition at 1 $\mu$ M ( $P < 0.05$ )	[54]
			IFN- $\gamma$	55% inhibition at 1 $\mu$ M ( $P < 0.01$ )	
Keratinocytes	UV-B light	N/A	TNF- $\alpha$	92% inhibition at 1 $\mu$ M ( $P < 0.01$ )	[54]
Chondrocytes	IL-1 $\beta$ + IL-6	Cytokine	IL-7 mRNA	60% inhibition at 1 $\mu$ M ( $P < 0.001$ )	[63]
Synoviocytes from RA patients	Spontaneous	N/A	TNF- $\alpha$	46% inhibition at 0.1 $\mu$ M ( $P < 0.001$ )	[56]
			IL-7 mRNA	45% inhibition at 1 $\mu$ M ( $P < 0.001$ )	[63]

<sup>a</sup> Apremilast plasma C<sub>min</sub> is  $\approx$ 0.5  $\mu$ M and C<sub>max</sub> is  $\approx$ 1.5  $\mu$ M based on a 24-week study of subjects with psoriasis treated with 30 mg BID.

CCL, chemokine (C-C motif) ligand; CXCL, chemokine (C-X-C motif) ligand; Fc $\gamma$ R, Fc immunoglobulin G receptor; HUVEC, human umbilical vein endothelial cells; IFN- $\gamma$ , interferon gamma; IgG, immunoglobulin G; IL, interleukin; LPS, lipopolysaccharide; LTB4, leukotriene B4; mRNA, messenger ribonucleic acid; NK, natural killer; PBMC, peripheral blood mononuclear cells; PMN, polymorphonuclear cells; RA; rheumatoid arthritis; TCR, T cell receptor; TNF- $\alpha$ , tumor necrosis factor alpha; TLR4, toll-like receptor 4; TLR2, toll-like receptor 2; UV-B, ultraviolet-B.

## 5. Apremilast pharmacology in nonclinical models and cell types relevant to arthritis

In human rheumatoid synovial membrane cells, apremilast reduced spontaneous TNF- $\alpha$  production in a concentration-dependent manner [56]. In two murine models of arthritis (anti-type II collagen monoclonal antibody and immunization with type II collagen), apremilast significantly reduced the clinical score and maintained a healthy joint architecture in a dose-dependent manner. Histopathological examination of the affected joints in the collagen antibody-induced arthritis model indicated that apremilast reduced the synovial hyperplasia, synovial villus formation, fibrin deposition, inflammatory infiltrate in the synovial membrane, pannus formation, cartilage disruption hyaline cartilage destruction, and subchondral bone destruction [56]. In subsequent studies, treatment of human T cells with apremilast resulted in partial inhibition of IL-2, IL-4, IL-13, IFN- $\gamma$ , TNF- $\alpha$ , CXCL10, CCL3, and CCL4. By comparison, etanercept inhibited only TNF- $\alpha$ , IL-13, and CXCL10 production, while the potent immunosuppressive agent cyclosporine A inhibited all cytokines and chemokines with greater potency than apremilast. Methotrexate had no effect. While apremilast reduced T cells TNF- $\alpha$  production by 70%, etanercept and cyclosporine inhibited TNF- $\alpha$  by 90% to 95%, demonstrating that the TNF- $\alpha$  inhibition by apremilast is only partial, as opposed to the near complete inhibition observed with the biologic or immunosuppressive agent.

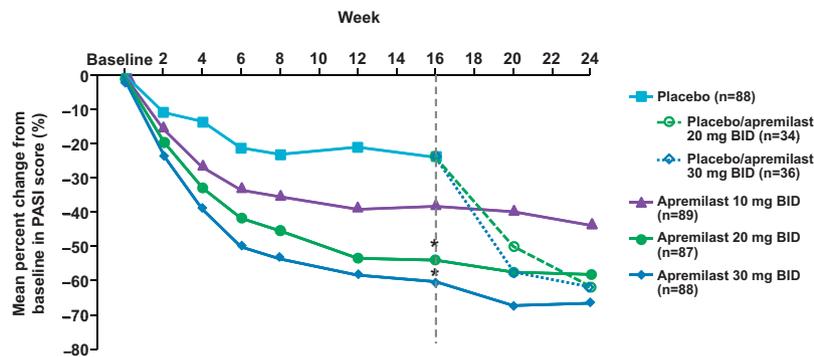
The cytokine IL-7 has recently been shown to play a prominent role in inflammatory joint diseases, such as arthritis, and in bone damage. IL-7 is a potent pleiotropic immunostimulatory cytokine produced by stromal cells such as chondrocytes and synoviocytes, and has historically been known to be a pivotal role in T cell development [57]. Blockade of the IL-7 receptor in the mouse model of collagen-induced arthritis potently inhibited joint inflammation and destruction in association with specific reductions of T cell-associated cytokines, T cell numbers, and other mediators of inflammation and tissue destruction [58]. In patients, IL-7 mRNA levels are elevated in spondylarthritic and RA synovial tissue samples, but are lower in osteoarthritis samples. At the protein level, synovial fluid IL-7 protein levels were higher in spondylarthritic than in RA, despite lower levels of TNF and IL-1 $\beta$  [59]. Methotrexate is a known inhibitor of IL-7 production, as reduced levels of IL-7 in the serum are associated with disease suppression in RA patients [60]. Importantly, transgenic mice overexpressing IL-7 have been shown to develop osteopenia and increased bone resorption, evidence of the osteoclastogenic effects of IL-7 [61]. Furthermore, IL-7 and IL-7 receptor are co-expressed in RA synovial tissue lining, and IL-7 has been found to mediate RA pathogenesis by inducing proangiogenic factor production by macrophages and endothelial cells [62]. In chondrocytes, apremilast was found to significantly reduce IL-7 gene expression in vitro in a dose-dependent manner. The inhibition of IL-7 by apremilast was more potent than that caused by etanercept or methotrexate, but not prednisolone [63]. Additionally, in RA patient derived synovial fibroblasts in vitro, apremilast significantly inhibited IL-7 mRNA expression, while etanercept, methotrexate, and prednisolone had no significant effect [63]. Taken together these data suggest that apremilast may be able to interfere with the inflammatory loop in the arthritic synovium created by the chondrocyte and synoviocyte production of IL-7, and the responding T cells that produce additional inflammatory cytokines and chemokines. Therefore apremilast may modulate the inflammatory response of both immune and non-immune cells within the arthritic synovium. A summary of the effects of apremilast on various cell types related to arthritis pathophysiology is presented in Table 1.

## 6. Clinical profile of the PDE4 modulator apremilast and linkage to the mechanism of psoriatic disease

Several characteristics of apremilast contribute to its differentiation from other PDE4 modulators. Unlike cilomilast, which has demonstrated 10-fold more selectivity for PDE4D (versus PDE A, B, or C), apremilast does not demonstrate any marked selectivity for the PDE4D subfamily [55]. This may be clinically important, because the PDE4D isozyme has been associated with the behavioral correlate of emesis in mice [64]. The lack of PDE4D selectivity of apremilast may in part explain its improved therapeutic index, with respect to gastrointestinal side effects, compared with cilomilast in nonclinical models [65]. In the ferret, apremilast inhibited lipopolysaccharide-induced lung neutrophilia at doses below the threshold emetic dose. In contrast, cilomilast inhibited lipopolysaccharide-induced lung neutrophilia at doses that were equivalent to the threshold emetic dose. In this model, apremilast exhibited a therapeutic index of 12, in comparison to a therapeutic index <1 with cilomilast [65]. Furthermore, while apremilast reduced zymosan-induced polymorphonuclear production of IL-8 with an IC<sub>50</sub> value of 94 nM [55], cilomilast blocked zymosan-induced IL-8 production by human neutrophils less potently than apremilast, with an IC<sub>50</sub> of approximately 700 nM [55,66]. Through the reduction of IL-8 production, apremilast may help to reduce the infiltration of neutrophils into resident, inflamed tissue typically triggered by the presence of IL-8 [55]. Apremilast also is associated with few behavioral effects seen with other PDE4 modulators, such as rolipram, in animal models. In a comparative preclinical investigation, mice exhibited significantly increased immobility ( $P < 0.001$ ), reduced grooming, and reduced locomotion ( $P < 0.05$ ) with rolipram, but no significant changes in any of these measures of lethargy were detected with apremilast [56].

Based on the positive findings from preclinical investigations, apremilast is in clinical development as an orally administered agent for a number of chronic inflammatory diseases, including psoriasis and psoriatic arthritis. In early-stage studies and placebo-controlled studies in subjects with psoriasis, apremilast has shown the capacity to modulate expression of inflammatory mediators, as well as significant therapeutic activity, and an acceptable tolerability profile. In an open-label study in subjects with moderate to severe plaque psoriasis treated for 29 days with apremilast 20 mg QD [49], CD11c cell (myeloid dendritic cells) were reduced from baseline by 18.5% and 40.2% in the dermis and epidermis, respectively, within lesional skin biopsies taken at day 0 and day 29. In the lipopolysaccharide-stimulated whole blood ex vivo cytokine production assay, TNF- $\alpha$  production was partially decreased in all subjects. Epidermal thickness was reduced by a mean of 20.5% from baseline at day 29. Nine of the 17 (52.9%) subjects had at least a one-point improvement in their static Physician Global Assessment rating. Among responders (e.g. subjects with at least 20% reduction in epidermal thickness [ $N = 8$ ]), T cells were reduced by 28.8% in the dermis and 42.6% in the epidermis. Skin biopsies also showed a reduction in the expression of mRNA for iNOS after 2 or 4 weeks of treatment with apremilast. Of note, the phase III psoriasis program is using an apremilast dose of 30 mg twice daily. Therefore, in subjects with moderate to severe psoriasis, apremilast has been shown to reduce the infiltration of myeloid dendritic cells, the production of iNOS and TNF- $\alpha$ , and to reduce keratinocyte responses to this inflammation as evidenced by the reduction in epidermal thickness.

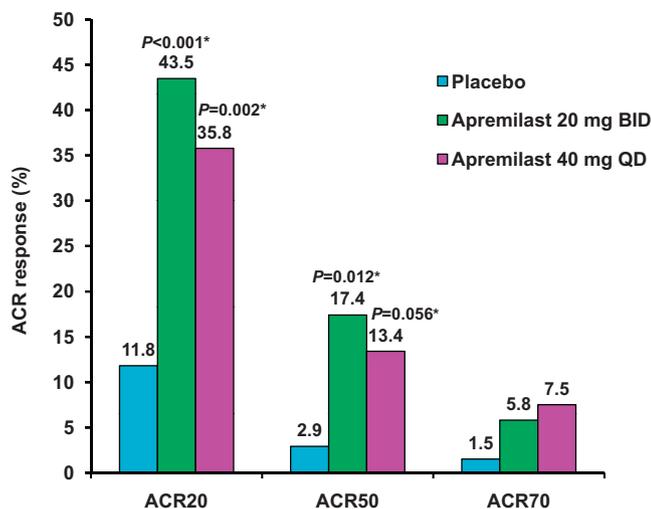
In phase II clinical studies, apremilast has been associated with improvement in a wide range of clinical outcomes for subjects with moderate to severe psoriasis. In a double-blind, placebo-controlled trial, Papp et al. [67] found that 24.4% of subjects treated with



**Fig. 2.** Percent change from baseline in Psoriasis Area and Severity Index (PASI) score over 24 weeks. Placebo/apremilast represents placebo patients re-randomized to apremilast treatment at week 16. \* $P < 0.001$  versus placebo.

apremilast 20 mg BID achieved a 75% or greater reduction in their Psoriasis Area and Severity Index (PASI) score ( $\geq$ PASI-75) compared with baseline after 12 weeks, versus 10.3% of subjects in the placebo arm ( $P = 0.023$ ). A 50% or greater reduction in their PASI score ( $\geq$ PASI-50) compared with baseline was achieved by 57% of subjects in the apremilast arm versus 23% in the placebo arm ( $P < 0.001$ ), and a 90% or greater reduction ( $\geq$ PASI-90) was achieved by 14% of subjects in the apremilast arm versus 5.7% in the placebo arm ( $P = 0.113$ ) [67]. In a phase IIb, double-blind, placebo-controlled, dose-finding study in subjects with moderate to severe psoriasis, a  $\geq$ PASI-75 was achieved by 11.2%, 28.7%, and 40.9% of subjects treated with apremilast 10, 20, or 30 mg BID, respectively versus 5.7% in the placebo arm (apremilast 20 mg BID versus placebo,  $P < 0.001$ ; apremilast 30 mg BID versus placebo,  $P < 0.001$ ) at week 16 [68] (Fig. 2). Treatment with apremilast also was associated with rapid and significant reductions in pruritus, based on a visual analog scale. Reductions in both PASI and pruritus visual analog scale scores were generally maintained over 24 weeks of treatment [68].

Apremilast also has been shown to improve clinical signs and symptoms in subjects with psoriatic arthritis. In a phase II, multicenter, randomized, double-blind, placebo-controlled, three-arm study of apremilast in adult subjects with active psoriatic arthritis, achievement of a 20% or greater improvement from baseline in American College of Rheumatology (ACR20) scores was



**Fig. 3.** Proportion of subjects achieving ACR20 at week 12 (intent to treat, last observation carried forward). ACR20, American College of Rheumatology criteria for 20% improvement; ACR50, American College of Rheumatology criteria for 50% improvement; ACR70, American College of Rheumatology criteria for 70% improvement. \*Versus placebo.

significantly greater with apremilast 20 mg BID (43.5%) and apremilast 40 mg QD (35.8%) compared with placebo (11.8%;  $P < 0.001$  and  $P = 0.002$ , respectively) at 12 weeks (Fig. 3) [50]. A significantly greater proportion of subjects treated with apremilast 20 mg BID achieved a 50% or greater improvement from baseline in ACR scores (17.4%) compared with placebo (2.9%) ( $P = 0.012$ ). Responses to apremilast were maintained over 24 weeks of treatment [50].

In studies of psoriasis and psoriatic arthritis, apremilast has shown acceptable safety and tolerability. With clinically effective doses of apremilast (20 mg BID, 30 mg BID, 40 mg QD) in subjects with moderate to severe plaque psoriasis or active psoriatic arthritis, the most common treatment-emergent adverse events were nausea, upper respiratory tract infection, nasopharyngitis, diarrhea, and headache. The majority of adverse events in both subject populations were of mild or moderate severity and did not lead to a dose reduction or treatment withdrawal. Importantly, no opportunistic infections have been reported with apremilast use [50,67,68].

Based on the results of phase II studies, apremilast 30 mg BID is currently being studied in phase III trials of psoriasis. In phase III studies of psoriatic arthritis and in phase II trials of rheumatoid arthritis and ankylosing spondylitis, apremilast doses of 20 mg BID and 30 mg BID are being tested. The psoriasis program, Efficacy and Safety Trial Evaluating the Effects of ApreMilast in Psoriasis (ESTEEM), includes two 52-week studies followed by 4-year long-term extensions. The psoriatic arthritis program, Psoriatic Arthritis Long-term Assessment of Clinical Efficacy (PALACE), consists of four 52-week double-blind, randomized, controlled studies, including a 24-week placebo-controlled phase, followed by long-term, open-label extensions (2–5 years), and will enroll both DMARD-experienced and DMARD-naïve subjects.

## 7. Conclusions

In recent years, researchers have gained key insights into the pathogenesis of psoriatic disease, which have highlighted the central role of aberrant immune cell signaling and chronic inflammation. It is believed that environmental triggering factors, such as stress, infection, injury, or drugs, initiate differentiation and activation of dendritic antigen-presenting cells, prompting their interaction with adaptive immune system T cells and promoting increased expression of numerous pro-inflammatory mediators. For reasons that are still not well understood, in patients with psoriatic disease, the initial inflammatory response to such triggers is not sufficiently countered by a balancing anti-inflammatory response, and the aberrant pro-inflammatory immune signaling becomes chronic. This ultimately results in changes among resident cells of the skin and joints with persistent clinical signs and symptoms.

The recognition by researchers of the need to restore normal homeostatic processes that control inflammatory signaling has opened the door to new therapeutic approaches to psoriasis management. To accomplish this, however, presents a considerable challenge, given the numerous molecular signals that mediate pro-inflammatory and anti-inflammatory signaling. One strategy that has received a great deal of research interest is the use of agents that modulate intracellular signaling and gene transcription. PDE4 inhibiting compounds have garnered much investigation as potential modulators of inflammatory signaling. As the chief family of enzymes responsible for degrading cAMP, and in turn altering activity of transcription factors like CREB and NF- $\kappa$ B, these compounds have demonstrated the ability to reduce cellular expression of pro-inflammatory markers that are usually elevated in psoriatic tissue, such as IL-23 and TNF- $\alpha$ , while simultaneously promoting expression of anti-inflammatory mediators such as IL-10. In addition, the expression of PDE4 within structural cell types (i.e. keratinocytes in psoriasis, synoviocytes in arthritis) permits apremilast to have a direct impact on the target tissue itself. Apremilast is an orally administered, targeted PDE4 inhibitor currently in clinical development that has shown the ability in preclinical and in vitro studies to lead to a more balanced inflammatory signaling phenotype. Clinical trials of apremilast in subjects with psoriasis or psoriatic arthritis have further demonstrated significant therapeutic benefits, marked by decreases in inflammatory mediators with the skin and joints, improvements in disease activity indices, and accompanied by an acceptable tolerability and safety profile. Compared with cilomilast and other PDE4 inhibiting compounds, apremilast appears to exert relatively few central nervous system effects and is not associated with any clear changes in behavior. On the basis of positive outcomes observed in phase II clinical trials, apremilast is currently being studied in phase III trials for psoriasis and psoriatic arthritis, as well as for phase II trials for rheumatoid arthritis and ankylosing spondylitis. If these clinical trials prove to be successful, apremilast will have defined oral targeted PDE4 inhibition as a novel treatment paradigm for these dermatological and rheumatological conditions.

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