Psoriasis is a chronic inflammatory disease that affects approximately 3% of the US population. Plaque psoriasis comprises 80% to 90% of cases, while pustular, erythrodermic, guttate, inverse, and palmoplantar disease are less common variants (Figure 1). Psoriatic skin manifestations range from localized to widespread or generalized disease with recurrent flares. Body surface area or psoriasis area and severity index (PASI) measurements primarily focus on skin manifestations and are important for evaluating disease activity and...
response to treatment, but they have inherent limitations: they do not capture extracutaneous disease activity, systemic inflammation, comorbid conditions, quality of life impact, or the economic burden of psoriasis.

A common manifestation of psoriasis is psoriatic arthritis (PsA), which can involve the nails, joints, ligaments, or tendons in 30% to 41% of affected individuals (Figure 2). A growing number of psoriasis-associated comorbidities also have been reported including metabolic syndrome; hyperlipidemia; cardiovascular disease; stroke; hypertension; obesity; sleep disorders; malignancy; infections; inflammatory bowel disease; and mental health disorders such as depression, anxiety, and suicidal ideation. Psoriatic disease also interferes with daily life activities and a patient’s overall quality of life, including interpersonal relationships, intimacy, employment, and work productivity. Finally, the total estimated cost of psoriasis-related health care is more than $35 billion annually, representing a substantial economic burden to our health care system and individual patients.

The overall burden of psoriatic disease has declined markedly in the last 2 decades due to revolutionary advances in our understanding of the immunopathogenesis of psoriasis and the subsequent development of improved therapies that predominantly interrupt IL-23/IL-17 cytokine signaling; however, critical knowledge and treatment gaps persist, underscoring the importance of ongoing clinical and research efforts in psoriatic disease. We review the working immune model of psoriasis, summarize related immune discoveries, and highlight recent therapeutic innovations that are shaping psoriatic disease management.

**Current Immune Model of Psoriatic Disease**

Psoriasis is an autoimmune T cell–mediated disease with negligible contributions from the humoral immune...
response. Early clinical observations reported increased inflammatory infiltrates in psoriatic skin lesions primarily consisting of both CD4+ and CD8+ T-cell populations.\textsuperscript{18,19} Additionally, patients treated with broad-acting, systemic immunosuppressive medications (eg, cyclosporine, oral corticosteroids) experienced improvement of psoriatic lesions and normalization of the immune infiltrates observed in skin biopsy specimens.\textsuperscript{20,21} These early clinical findings led to more sophisticated experimentation in xenotransplant models of psoriasis,\textsuperscript{22,23} which explored the clinical efficacy of several less immunosuppressive (eg, methotrexate, anti–tumor necrosis factor [TNF] biologics)\textsuperscript{24} or T cell–specific agents (eg, alefacept, abatacept, efalizumab).\textsuperscript{25-27} The results of these translational studies provided indisputable evidence for the role of the dysregulated immune response as the primary pathogenic process driving plaque formation; they also led to a paradigm shift in how the immunopathogenesis of psoriatic disease was viewed and paved the way for the identification and targeting of other specific proinflammatory signals produced by activated dendritic cell (DC) and T-lymphocyte populations. Among the psoriasis-associated cytokines subsequently identified and studied, elevated IL-23 and IL-17 cytokine levels in psoriatic skin were most closely associated with disease activity, and rapid normalization of IL-23/IL-17 signaling in response to effective oral or injectable antipsoriatic treatments was the hallmark of skin clearance.\textsuperscript{28} The predominant role of IL-23/IL-17 signaling in the development and maintenance of psoriatic disease is the central feature of all working immune models for this disease (Figure 3).

Psoriasis-Associated Genetic and Environmental Risk Factors

The exact sequence of events that lead to the initiation and formation of plaque psoriasis in susceptible individuals is still poorly understood; however, several important risk factors and key immune events have been identified. First, decades of genetic research have reported more than 80 known psoriasis-associated susceptibility loci,\textsuperscript{29} which explains approximately 50% of psoriasis heritability. The major genetic determinant of psoriasis, HLA-C*06:02 (formerly HLA-Cw6), resides in the major histocompatibility complex class I region on chromosome 6p21.3 (psoriasis susceptibility gene 1, PSORS1) and is most strongly associated with psoriatic disease.\textsuperscript{30} Less common psoriasis-associated susceptibility genes also are known to directly or indirectly impact innate and adaptive immune functions that contribute to the pathogenesis of psoriasis.

Second, several nongenetic environmental risk factors for psoriasis have been reported across diverse patient populations, including skin trauma/injury, infections, alcohol/tobacco use, obesity, medication exposure (eg, lithium, antimalarials, beta-blockers), and stress.\textsuperscript{31} These genetic and/or environmental risk factors can trigger the onset of psoriatic disease at any stage of life, though most patients develop disease in early adulthood or later (age range, 50–60 years). Some patients never develop psoriasis despite exposure to environmental risk factors and/or a genetic makeup that is similar to affected first-degree relatives, which requires further study.

Prepsoriatic Skin and Initiation of Plaque Development

In response to environmental stimuli and/or other triggers of the immune system, DC and resident IL-17-producing T-cell (T17) populations become activated in predisposed individuals. Dendritic cell activation leads to the upregulation and increase of several proinflammatory cytokines, including TNF, interferon (IFN) α, IFN-γ, IL-12, and IL-23. Tumor necrosis factor and IL-23 play a vital role in psoriasis by helping to regulate the polarization and expansion of T22 and T17 cells in the skin, whereas IL-12 promotes a corresponding type 1 inflammatory response.\textsuperscript{32} Increased IL-17 and IL-22 result in alteration of the terminal differentiation and proliferative potential of epidermal keratinocytes, leading to the early clinical hallmarks of psoriatic plaques. The potential contribution of overexpressed psoriasis-related autoantigens, such as LL-37/cathelicidin, ADAMTS15, and PLA2G4D,\textsuperscript{33} in the initiation of psoriatic plaques has been suggested but is poorly characterized.\textsuperscript{34} Whether these specific autoantigens or others presented by HLA-C variants found on antigen-presenting cells are required for the breakdown of immune tolerance and psoriatic disease initiation is highly relevant but requires further investigation and validation.

Feed-Forward Inflammation, Mature Psoriatic Plaques, and Resident Memory T Cells

In response to the upstream production of IL-23 by dermal DCs, high levels of IL-17 cytokines can be found in mature psoriatic plaques. The IL-17 family consists of 6 dimeric cytokines (IL-17A through IL-17F) that provide innate cutaneous protection against bacterial, viral, and fungal infectious agents, such as Candida albicans. Unlike other IL-17 isoforms, IL-17A and IL-17F share the same
receptor complex and have the highest structural homology of any pair (approximately 50% similar). The relative expression of IL-17F is higher than IL-17A in psoriasis, though IL-17A has been considered as the predominant IL-17 cytokine found in psoriatic skin lesions due to its higher potency.

Binding of IL-17A/F with the IL-17 receptor (IL-17R) on keratinocytes contributes to the development of psoriatic plaques by inducing epidermal hyperplasia via activation of CCAAT/enhancer-binding proteins β and δ, nuclear factor κB, and signal transducer and activator of transcription 1 gene (STAT1). This also increases the expression of other keratinocyte-derived proteins (eg, human β-defensins, S-100 proteins, LL-37, other antimicrobial peptides, IL-19, IL-36, IL-17C) and chemotactic factors (chemokine [C-C motif] ligand 20 [CCL20], chemokine [C-C motif] ligand 1/2/3/5/8 [CXCL1/2/3/5/8] or IL-8) that facilitate further activation and recruitment of T17 and helper T cell (T H1) lymphocytes, DCs, macrophages, and polymorphonuclear neutrophils (PMNs) into the skin. The resultant inflammatory circuit creates a self-amplifying or feed-forward immune response in the skin that leads to the hallmark clinical features of psoriasis and sustains the mature psoriatic plaque.

FIGURE 3. Working immune model of psoriasis. Early immune events include activation of dendritic cells (DCs) and IL-17–producing T cells (T17) in the prepsoriatic (or normal-appearing) skin of individuals who are genetically susceptible and/or have exposures to known psoriasis triggers. Activation of DC and T17 populations in the skin results in increased production of tumor necrosis factor (TNF), IL-23, and IL-17 cytokines (namely IL-17A and IL-17F), which work synergistically with other immune signals (IL-12, IL-22, IL-36, TNF, interferon [IFN]) to drive keratinocyte (KC) hyperproliferation. In response to upregulated IL-17 signaling, substantial increases in keratinocyte-derived proteins (antimicrobial peptides, IL-19, IL-36, IL-17C) and chemotactic factors (chemokine [C-C motif] ligand 20 [CCL20], chemokine [C-C motif] ligand 1/2/3/5/8 [CXCL1/2/3/5/8] or IL-8) facilitate further activation and recruitment of T17 and helper T cell (T H1) lymphocytes, DCs, macrophages, and polymorphonuclear neutrophils (PMNs) into the skin. The resultant inflammatory circuit creates a self-amplifying or feed-forward immune response in the skin that leads to the hallmark clinical features of psoriasis and sustains the mature psoriatic plaque.
body sites such as the scalp, buttocks, extremity extensor surfaces, umbilicus, or acral skin following specific stimuli or trauma (Koebner phenomenon or isomorphic response).44,45 It is not known if repeated stimuli or trauma induce disease formation via the activation of Treg cell populations; further study in large patient cohorts is needed, but this remains an intriguing area of study for durable treatment responses and potential cures for psoriasis.

Recent Discoveries in Psoriatic Disease

Remarkable treatment outcomes for psoriasis have been achieved with multiple selective IL-17 and IL-23 inhibitors (eTable). As demonstrated in several pivotal phase 3 clinical trials for members of these classes of medications, the majority of treated psoriasis patients achieved PASI90 clearance.46 Due to their more favorable dosing schedule (ie, fewer injections) and ability to induce a durable remission-like treatment response, IL-23 inhibitors have become the preferred treatment class for cutaneous disease, while IL-17 inhibitors may be preferred when treating patients with both plaque psoriasis and PsA.47,48 Nevertheless, the complexity of this disease is punctuated by treated patients who do not adequately respond to selective IL-23/IL-17 blockade.49 Recent and emerging treatments may shed light on these recalcitrant cases and will add to the rapidly growing arsenal of available psoriasis therapies.

The Role of IL-17F in Psoriasis and Other Inflammatory Skin Diseases

Dysregulation of IL-17A and IL-17F is associated with several chronic inflammatory conditions, such as psoriasis and PsA.35,50 Both cytokines, either as homodimers or heterodimers, can selectively bind to the heterodimeric IL-17R formed by the IL-17RA and IL-17RC subunits.35 IL-17F and IL-17C also can synergize with TNF and other cytokines to promote and support the self-sustaining inflammatory circuits in mature psoriatic plaques, though their inflammatory effects in the skin are more limited than IL-17A.91,92 Therefore, incomplete blockade of IL-17 signaling (ie, unopposed IL-17F and IL-17C) represents a potential mechanism to explain the persistence of psoriasis in patients treated with selective IL-17A inhibitors. This hypothesis is supported by reports of psoriasis patients who have inadequate clinical responses to selective IL-17A inhibition but subsequently improve with IL-17R blockade, which results in disruption of IL-17A as well as IL-17C/E/F cytokine signaling. This formed the basis for further study into the specific role of IL-17F in psoriatic disease and any potential therapeutic benefits associated with its inhibition.

Recently approved in the European Union, Canada, Australia, Japan, the United Kingdom, and the United States for moderate to severe psoriasis, bimekizumab is a novel humanized IgG antibody that selectively inhibits both IL-17A and IL-17F cytokines.53 Specifically, bimekizumab simultaneously prevents binding of IL-17A/A, IL-17A/F, and IL-17F/F dimers with the IL-17R. Compared to other IL-17 and IL-23 biologic therapies, bimekizumab (320 mg) achieved relatively higher response rates for PASI75, PASI90, and PASI100.49 Neutralization of IL-17A and IL-17F by bimekizumab also resulted in more complete suppression of cytokine responses and PMN chemotaxis than either cytokine alone in treated PsA patients,54 which is notable because of the incremental benefits of recent IL-23 and IL-17 inhibitors on inflammatory arthritis symptoms in contrast to the substantial improvements observed for cutaneous disease with those same agents.

The primary disadvantage of bimekizumab and its more complete blockade of the IL-17 signaling pathway is that treated patients have a substantially increased risk for oral candidiasis (>10%).55 However, the precise link between candidiasis and IL-17 blockade is not yet fully understood because other targeted agents that also broadly suppress IL-17 signaling (ie, IL-17R, IL-23 inhibitors) are associated with much lower rates of candidiasis.56-58 Bimekizumab also is being investigated as a novel therapy for hidradenitis suppurativa and will provide important reference information regarding the role for bispecific biologic agents in the treatment of chronic inflammatory skin diseases.59

IL-36 Signaling and Generalized Pustular Psoriasis

Recent genetic and clinical studies have expanded our understanding of the role of IL-36 signaling in the immunopathogenesis of pustular psoriasis variants. Generalized pustular psoriasis (GPP) is a rare distinct psoriasis subtype characterized by the recurrent development of widespread erythema, superficial sterile pustules, and desquamation. Systemic symptoms such as fever, malaise, itching, and skin pain accompany acute GPP flares.60 Generalized pustular psoriasis is more common in female patients (in contrast with plaque psoriasis), and acute flares may be caused by multiple stimuli including infections, hypocalcemia, initiation or discontinuation of medications (eg, oral corticosteroids), pregnancy, or stress.51-52,55 Flares of GPP often require emergency or inpatient care, as untreated symptoms increase the risk for severe health complications such as secondary infections, sepsis, or multisystem organ failure.63 The prevalence of GPP is estimated to be approximately 1 in 10,000 individuals in the United States,64-67 with mortality rates ranging from 0 to 3.3 deaths per 100 patient-years.67

In contrast to plaque psoriasis, aberrant IL-36 signaling is the predominant driver of GPP. IL-36 is a member of the IL-1 cytokine family that includes three IL-36 agonists (IL-36α, IL-36β, IL-36γ) and 1 endogenous antagonist (IL-36Ra, encoded by IL36RN).68 The immunopathogenesis of GPP involves dysregulation of the IL-36–chemokine–PMN axis, resulting in unopposed IL-36 signaling and the subsequent recruitment and influx of
PMNs into the epidermis. IL36RN mutations are strongly associated with GPP and result in impaired function of the IL-36Ra protein, leading to unopposed IL-36 signaling. However, approximately two-thirds of GPP patients lack identifiable gene mutations, suggesting other immune mechanisms or triggers causing upregulated IL-36 signaling. In response to these triggers, increased IL-36 cytokines released by keratinocytes bind to the IL-36R, resulting in substantial keratinocyte hyperproliferation, increased IL-36 levels, and the expression of hundreds of additional inflammatory signals (eg, IL-17C, antimicrobial peptides, TNF, IL-6). Increased IL-36 levels also drive the production of PMN chemotactic proteins (eg, CXCL1/2/3/5/6/8 and CXCR1/2) and act synergistically with IL-17 cytokines to create an autoamplifying circuit that is analogous to the feed-forward inflammatory loop in plaque psoriasis. Biopsies of involved GPP skin reveal increased expression of IL-36 in the uppermost layers of the epidermis, which creates a gene expression gradient that acts as a strong attractant for PMNs and forms the basis for the hallmark pustular lesions observed in GPP patients.

Until recently, treatment strategies for GPP involved the off-label use of topical, oral, or biologic therapies approved for plaque psoriasis, which often was associated with variable or incomplete disease control. In September 2022, the US Food and Drug Administration (FDA) approved intravenous spesolimab as a first-in-class humanized monoclonal IgG1 antibody for the treatment of GPP flares in adults. Spesolimab binds to IL-36R and prevents its activation by its endogenous agonists. A phase 2, randomized, 12-week clinical trial (Effisayil-1) evaluated the efficacy and safety of a single 900-mg intravenous dose of spesolimab followed by an optional second dose 1 week later for inadequate treatment responses in 53 enrolled GPP patients (2:1 treatment to placebo randomization). Remarkably, more than half (19/35 [54%]) of GPP patients experienced complete resolution of pustules (FDA physician global assessment subscore of 0 [range, 0–4]) and showed sustained efficacy out to week 12 after just 1 or 2 doses of spesolimab. Overall, the safety profile of spesolimab was good; asthenia, fatigue, nausea, vomiting, headache, pruritus, infusion-related reaction and symptoms, and mild infections (eg, urinary tract infection) were the most common adverse events reported.

Imsidolimab, a high-affinity humanized IgG4 monoclonal antibody that binds and blocks activation of IL-36R, also has completed phase 2 testing with phase 3 study results expected in early 2024. The rapid onset of action and overall safety of imsidolimab was in line with and similar to spesolimab. Future approval of imsidolimab would add to the limited treatment options available for GPP and has the additional convenience of being administered to patients subcutaneously. Overall, the development of selective IL-36R inhibitors offers a much-needed therapeutic option for GPP and illustrates the importance of translational research.

Role of Tyrosine Kinase in Psoriatic Disease

The Janus kinase (JAK) enzyme family consists of 4 enzymes—tyrosine kinase 2 (TYK2), JAK1, JAK2, and JAK3—that function as intracellular transduction signals that mediate the biologic response of most extracellular cytokines and growth factors. Critical psoriasis-related cytokines are dependent on intact JAK-STAT signaling, including IL-23, IL-12, and type 1 IFNs. In 2010, a genome-wide association identified TYK2 as a psoriasis susceptibility locus, and loss-of-function TYK2 mutations confer a reduced risk for psoriasis. Unlike other JAK isoforms, TYK2 mediates biologic functions that are highly restricted to the immune responses associated with IL-23, IL-12, and type 1 IFN signaling. For these reasons, blockade of TYK2 signaling is an attractive therapeutic target for the potential treatment of psoriatic disease.

In September 2022, the FDA approved deucravacitinib as a first-in-class, oral, selective TYK2 inhibitor for the treatment of adult patients with moderate to severe plaque psoriasis. It was the first FDA approval of an oral small-molecule treatment for plaque psoriasis in nearly a decade. Deucravacitinib inhibits TYK2 signaling via selective binding of its unique regulatory domain, resulting in a conformational (allosteric) change that interferes with its active domain. This novel mechanism of action limits the unwanted blockade of other broad biologic processes mediated by JAK1/2/3. Of note, the FDA did not issue any boxed warnings for deucravacitinib as it did for other FDA-approved JAK inhibitors.

In a head-to-head, 52-week, double-blind, prospective, randomized, phase 3 study, deucravacitinib showed clear superiority over apremilast for PASI75 at week 16 (53.0% [271/511] vs 39.8% [101/254]) and week 24 (58.7% [296/504] vs 37.8% [96/254]). Clinical responses were sustained through week 52 and showed efficacy for difficult-to-treat areas such as the scalp, acral sites, and nails. Other advantages of deucravacitinib include once-daily dosing with no need for dose titration or adjustments for renal insufficiency as well as the absence of statistically significant differences in gastrointestinal tract symptoms compared to placebo. The most common adverse effects included nasopharyngitis, upper respiratory tract infections, headache, diarrhea, and herpes infections. The potential benefit of deucravacitinib for PsA and psoriatic comorbidities remains to be seen, but it is promising due to its simultaneous disruption of multiple psoriasis-related cytokine networks. Several other TYK2 inhibitors are being developed for psoriatic disease and related inflammatory conditions, underscoring the promise of targeting this intracellular pathway.

Aryl Hydrocarbon Receptor Agonism

Topical steroids are the mainstay treatment option for localized or limited plaque psoriasis due to their potent immunosuppressive effect on the skin and relatively low cost. Combined with vitamin D analogs, topical steroids
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result in marked improvements in disease severity and improved tolerability. However, chronic use of topical steroids is limited by the need for twice-daily application, resulting in poor treatment compliance; loss of efficacy over time; risk for steroid-induced skin atrophy on special body sites; and patient concerns of potential systemic effects. The discovery of novel drug targets amenable to topical inhibition is needed.

Dysregulated aryl hydrocarbon receptor (AHR) levels have been reported in atopic dermatitis and psoriasis. Aryl hydrocarbon receptors are ubiquitously expressed in many cell types and play an integral role in immune homeostasis within the skin, skin barrier function, protection against oxidative stressors, and regulation of proliferating melanocytes and keratinocytes. They are widely expressed in multiple immune cell types (e.g., antigen-presenting cells, T lymphocytes, fibroblasts) and modulate the differentiation of T17 and T22 cells as well as their balance with regulatory T-cell populations. In keratinocytes, AHR helps to regulate terminal differentiation, enhance skin barrier integrity via AHR-dependent filaggrin (FLG) expression, and prevent transepidermal water loss. The mechanisms by which AHR ligands lead to the upregulation or downregulation of specific genes is intricate and highly context dependent, such as the specific ligand and cell type involved. In preclinical studies, AHR-deficient mice develop psoriasiform skin inflammation, increased IL-17 and IL-22 expression, and abnormal skin barrier function. Keratinocytes treated with AHR ligands in vitro modulated psoriasis-associated inflammatory cytokines, such as IL-6, IL-8, and type I and II IFNs. The use of coal tar, one of the earliest historical treatments for psoriasis, is thought to activate AHRs in the skin via organic compound mixtures containing polyaromatic hydrocarbons that help normalize the proinflammatory environment in psoriatic skin.

In June 2022, the FDA approved tapinarof as a first-in-class, topical, nonsteroidal AHR agonist for the treatment of plaque psoriasis in adults. Although the exact mechanism of action for tapinarof has not been fully elucidated, early studies suggest that its primary function is the activation of AHR, leading to reduced T-cell expansion and T17 cell differentiation. In the imiquimod mouse model, cytokine expression of IL-17A, IL-17F, IL-19, IL-22, IL-23A, and IL-1β in psoriasiform skin lesions were downregulated following tapinarof treatment.

In humans, tapinarof treatment is associated with a remittive effect, in which the average time for tapinarof-treated psoriasis lesions to remain clear was approximately 4 months. Preliminary research investigating the mechanism by which tapinarof induces this remittive effect is ongoing and may involve the reduced activation and influx of T17 and Trm populations into the skin. However, these preclinical studies were performed on healthy dermatome-derived skin tissue cultured in T17-skewing conditions and needs to be replicated in larger samples sizes using human-derived psoriatic tissue. Alternatively, a strong inhibitory effect on IL-23 cytokine signaling may, in part, explain the remittive effect of tapinarof, as an analogous response is observed in patients who start and discontinue treatment with selective IL-23 antagonists. Regardless, the once-daily dosing of tapinarof and sustained treatment response is appealing to psoriasis patients. Tapinarof generally is well tolerated with mild folliculitis (>20% of patients) and contact dermatitis (5% of patients) reported as the most common skin-related adverse events.

New Roles for Phosphodiesterase 4 Inhibition

Phosphodiesterases (PDEs) are enzymes that hydrolyze cyclic nucleotides (e.g., cyclic adenosine monophosphate) to regulate intracellular secondary messengers involved in the inflammatory response. One of several enzymes in the PDE family, PDE4, has been shown to have greater activity in psoriatic skin compared to healthy skin. Phosphodiesterase inhibitors decrease the degradation of cyclic adenosine monophosphate, which triggers protein kinase A to downregulate proinflammatory cytokines (e.g., TNF-α, IL-6, IL-17, IL-12, IL-23) and increased expression of anti-inflammatory signals such as IL-10. Apremilast, the first oral PDE4 inhibitor approved by the FDA for psoriasis, offered a safe alternative to traditional oral immunosuppressive agents that had extensive risks and potential end-organ adverse effects. Unfortunately, apremilast demonstrated modest efficacy for psoriatic disease (better efficacy in the skin vs joint manifestations) and was supplanted easily by next-generation targeted biologic agents that were more efficacious and lacked the troublesome gastrointestinal tract adverse effects of PDE4 inhibition.

Crisaborole became the first topical PDE4 inhibitor approved in the United States in December 2016 for twice-daily treatment of atopic dermatitis. Although phase 2 trial results were reported in psoriasis, this indication was never pursued, presumably due to similar improvements in primary outcome measures at week 12, compared to placebo (ClinicalTrials.gov Identifier NCT01300052).

In July 2022, the first topical PDE4 inhibitor indicated for plaque psoriasis was approved by the FDA—roflumilast cream 0.3% for once-daily use in individuals 12 years and older. Roflumilast was found to be clinically efficacious as early as 2 weeks after its use in an early-phase clinical trial. In 2 phase 3 clinical trials (DERMIS-1 and DERMIS-2), roflumilast significantly increased the proportion of patients achieving PASI75 at week 8 compared to vehicle (39%-41.6% vs 5.3%-7.6%, respectively) ($P<.001$). Overall, this nonsteroidal topical therapy was found to be well tolerated, with infrequent reports of application site pain or irritation as adverse events. Similar to tapinarof, patients can apply roflumilast on all body surface areas including the face, external genitalia, and other intertriginous areas. Importantly, the
broad immune impact of PDE4 inhibition suggests that topical rolflumilast likely will be an effective treatment for several additional inflammatory conditions, including seborheic dermatitis and atopic dermatitis, which would expand the clinical utility of this specific medication.

Conclusion
In the last 2 decades, we have witnessed a translational revolution in our understanding of the underlying genetics and immunology of psoriatic disease. Psoriasis is widely considered one of the best-managed inflammatory conditions in all of medicine due to the development and availability of highly targeted, effective topical and systemic therapies that predominantly disrupt IL-23/IL-17 cytokine signaling in affected tissues. However, future clinical studies and laboratory research are necessary to elucidate the precise cause of psoriasis as well as the underlying genetic and immune signaling pathways driving less common clinical variants and recalcitrant disease.

REFERENCES
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## Novel Biologic and Topical Therapies for the Treatment of PsO and PsA

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Abbreviations: AHR, aryl hydrocarbon receptor; GPP, generalized pustular psoriasis; IL-17R, IL-17 receptor; IL-36R, IL-36 receptor; IV, intravenous; JAK, Janus kinase; PDE4, phosphodiesterase 4; PsA, psoriatic arthritis; PsO, plaque psoriasis; subQ, subcutaneous; TNF, tumor necrosis factor; TYK2, tyrosine kinase.