We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Developing Novel Molecular Targeted Therapeutics for Topical Treatment of Psoriasis

Suxing Liu, Di Li and Weikang Tao

Abstract

Psoriasis is a chronic inflammatory skin disorder. The prevalence of psoriasis is estimated at approximately 100 million people worldwide. In mild-to-moderate, as well as moderate-to-severe, psoriasis, 70–80% of patients start with topical agents and continue to use them with other active therapies. This group of patients can benefit from topical treatment with minimal systemic exposure. The expression levels of IL-23 and IL-17 are upregulated in psoriatic skin compared with non-lesional skin, associated with psoriasis pathogenesis. The skin epidermal proliferation and psoriasis are caused by overactive Th17 cells, which are promoted and stabilized by the activated IL-23 receptor, forming part of the positive feedback loop. FDA approved biologics in IL-23/IL-17 axis (ustekinumab, guselkumab, risankizumab, tildrakizumab, ixekizumab, secukinumab and brodalumab) demonstrated superior clinical efficacy in the systemic treatment of moderate-to-severe psoriasis, providing the clinical proof of concept of the IL-23/IL-17 axis as a major immune pathway underlying the pathophysiology of psoriasis. However, due to the large size and poor permeability into skin, biologics are not suitable to deliver via topical route. Current topical treatments of mild-to-moderate psoriasis are corticosteroids and vitamin D analogues, which have limited efficacy with significant side effects so that patients must avoid long-term use. This chapter reviews current molecular targeted therapeutics under development for topical treatment of psoriasis.

Keywords: psoriasis, topical drug, TH17, IL-23, IL-17, small molecule inhibitor

1. Introduction

Psoriasis is a chronic immune cell-mediated inflammatory skin disease characterized by the formation of scaly indurated erythema occurring most commonly on the elbows, knees, scalp, and lower back, but any skin surface can be involved [1]. The highly visible condition greatly affects people's quality of life that can be stigmatizing. People with psoriasis are at an increased risk of developing other chronic and serious health conditions. Comorbidities include psoriatic arthritis, inflammatory bowel disease, hypertension, diabetes, obesity, and depression. The worldwide prevalence of psoriasis is estimated to be 2–4%, rising up to 9.7% in Scandinavian countries [2, 3].

Psoriasis can be classified into mild, moderate, or severe disease according to the Psoriasis Area and Severity Index (PASI). Treatment choices are often based on the severity of disease: mild disease often managed with topical therapy, and moderate-to-severe disease requiring systemic therapy for control, often with concomitant topical therapy [4–6]. Effects of systemic therapy in synergy with topical agents may help reduce the burden and achieve better quality of life that psoriasis patients deserve. In mild-to-moderate, as well as moderate-to-severe, psoriasis, 70–80% of patients start with topical agents and continue to use them with other active therapies.

Currently, high-potency topical glucocorticoid and vitamin D derivatives are the main treatments for psoriasis [7–9]. Topical glucocorticoids are effective but their use is limited to no more than 2–8 weeks due to their long-term side effects, such as atrophy [10]. This is particularly true in more sensitive areas, such as the face or intertriginous areas. There are numerous reports of low satisfaction for these topical agents [11]. Hence, there remains great unmet medical needs for developing a highly efficacious and safe topical treatment in psoriasis.

2. IL-23/IL-17 axis is a major immune pathway in the development of psoriasis

2.1 Psoriasis is a TH17-driven disease

In psoriatic skin, immune response is overactive. Excess amounts of cytokines were produced, which caused prolonged inflammation and abnormal proliferation of keratinocytes. In recent decades, genetic and immunological studies have made progress in dissecting the mechanisms of psoriasis. Psoriasis was previously thought to be an interferon (IFN)- γ -producing T helper (TH) 1-driven autoimmune inflammatory disease [12, 13]. However, the discovery of TH17 cells shifted the view of psoriasis as an TH17-dependent pathology rather than TH1 cells [12–14].

IFN- γ is increased in serum from psoriasis patients and its mRNA is elevated in skin lesions [15, 16]. It was hypothesized that IFN γ blockade could decrease disease activity due to the appreciation of elevated IFN- γ expression in psoriasis. A neutralized humanized anti-IFN- γ antibody, HuZAF, was developed and tested in two small pilot studies between 2001 and 2003 [17]. In the study that was designed to determine the efficacy of miltidose HuZAF, of all 10 patients treated four times with 10 mg/kg of HuZAF, only 1 patient (10%) achieved a significant clinical response. The expression of CXCL9 was significantly suppressed by HuZAF through week 12. This finding suggests IFN- γ was successfully blocked by HuZAF in these patients since CXCL9 is heavily regulated by IFN- γ . The limited clinical efficacy of IFN γ blockade by HuZAF in patients with psoriasis suggest that infiltration of TH1 cells in psoriatic plaque likely contribute little to the pathogenesis of this disease.

The naive T cells are differentiated into TH1, TH2, TH17, or Treg cells depending on specific cytokines released by antigen-presenting cells and T-cell receptor stimulation and costimulation. The differentiation of TH17 cells are induced by interleukin (IL)-6, transforming growth factor (TGF)- β , and IL-21 [18–20]. Maintenance of TH17 population requires IL-23, a heterodimeric cytokine expressed by macrophages and dendritic cells [21, 22]. The intracellular transcription factors ROR γ t and STAT3 are also critical in the development of TH17 cells. Binding of IL-23 to IL-23 receptor (IL23R) attracts a heterodimer of kinase JAK2 and TYK2 and induces phosphorylation of STAT3, which enhances ROR γ -mediated transcription of IL-17A and IL-17F [23, 24]. TGF- β 1 is

abundantly expressed in plasma and scales from psoriatic lesions and transgenic mice that overproduce human TGF- β 1 in basal keratinocytes exhibit classic signs of psoriasis [25]. Similar observations were made with STAT3, which is overproduced in psoriasis, and its transgenic mice also exhibit psoriasis-like phenotypes [26]. Under the regulation of IL-23, activated TH17 cells in the skin produce high levels of IL-17, which is often referred to as the IL-23/IL-17 axis.

2.2 IL-23 stimulates TH17 cell survival and proliferation

On developing TH17 cells, the expression of IL-23R is induced by intracellular signaling through ROR γ t and STAT3 and extracellular TGF- β 1. The expression of IL-23R then promotes responsiveness to IL-23, which is the key cytokine in the survival and proliferation of TH17 cells [27, 28]. In psoriasis lesions, IL-23 is overproduced by dendritic cells and keratinocytes [29–31].

The importance of IL-23 in psoriasis has been confirmed by genetic studies. Polymorphisms in both subunits of IL-23, IL23A (p19) and IL12B (p40), and IL23R have been reported to be associated with an increased risk of psoriasis in North Americans, Europeans and Asians [32, 33]. A common risk haplotype of IL-23R, proline at amino acid 310 and arginine at amino acid 381, was identified. A single amino acid change from arginine to glutamine at amino acid 381 in IL-23R was found to be protective against psoriasis. Interestingly, this amino acid is located at the JAK2 kinase-binding domain of IL-23R. It is likely the change to glutamine breaks the IL-23R signaling and blocks inflammatory response induced by TH17 cell. In mouse studies, intradermal injection of recombinant IL-23 in normal-appearing skin induces skin inflammation and produces erythematous, thick and scaly skin with histologic features reminiscent of psoriasis [34], and IL-23 deficient mice were resistant to imiquimod-induced psoriasis-like inflammation [35]. Similarly, mice lacking IL-23 are resistant to experimental autoimmune encephalomyelitis (EAE) [21].

IL-23 belongs to the IL-12 family of cytokines and consists of two subunits: p19 and p40. P19 is unique for IL-23 and p40 is shared with IL-12. There are several lines of evidence to demonstrate the central role of IL-23, but not IL-12, in the pathogenesis of psoriasis [14]. The high expression of p19 and p40, but not IL-12 specific p35 expression, was observed in psoriatic lesions as compared to nonlesional skin [36]. Mice lacking the p35 subunit of IL-12 (*Il12a*^{-/-}) or the IL-12-respectific receptor subunit (*Il12rb2*^{-/-}) significantly increased skin inflammation, consistent with the observation in the EAE model of multiple sclerosis that IL-12 knockout mice led to worsening inflammation [21, 37]. In transgenic mice, overexpression of individual subunits of IL-23 leads to inflammation [38, 39]. Ubiquitous transgenic expression of the IL-23 subunit p19 induced a striking phenotype characterized by multiorgan inflammation, runting, infertility and death before 3 month of age [38]. Furthermore, p40 transgenic mice constitutively produce IL-23 (p19/p40), but not IL-12 (p35/p40), in basal keratinocytes by secretion of transgenic p40 with endogenous p19 [39]. p40 transgenic mice cause an inflammatory skin disease, similar to that of intradermal injection of recombinant IL-23 in mice, confirming the provital role of IL-23, but not IL-12, in psoriasis pathogenesis.

2.3 IL-17 is a central proinflammatory effector cytokine in psoriasis

IL-23 is required for autoimmune inflammation mediated by TH17 cells and produces large amounts of IL-17 *in vivo* [40]. IL-23 injection into skin of wild-type

mice induces psoriasis-like symptoms, but not in IL-17 knockout mice, and if the wild-type mice are pre-treated with IL-17 antibody, IL-23-induced disease is blocked, suggesting that IL-17 is downstream of IL-23 and critical role in psoriasis pathogenesis [12].

Among six isoforms of IL-17, IL-17A and IL-17F are the most pathogenic in psoriasis [31]. IL-17A is often referred to as IL-17, for which the TH17 cell lineage is named. Besides TH17 cells, a large number of other skin cells also produce IL-17, including $\gamma\delta$ T cells, $\alpha\beta$ T cells, neutrophils, mast cells, ILC3s and Tc17 cells. Some production is independent of IL-23 [12]. In psoriatic skin, IL-17 expression is higher, and the number of TH17 cells, $\gamma\delta$ T cells, Tc17 cells were all greatly increased compared to normal skin [30, 41]. Genes that are up-regulated in keratinocytes treated by IL-17A *in vitro*, are corresponded to the genes up-regulated in psoriasis lesions, and the overlap is bigger than that by TNF- α or IFN- γ [42]. In response to IL-17, keratinocytes produce a variety of antimicrobial peptides (AMPs) and chemokines. They induce inflammation and neutrophil recruitment and lead to hyperproliferation of the epidermis and aberrant differentiation of keratinocytes [43].

Even in nonlesional skin from psoriasis patients, expression of IL-17-downstream genes is higher compared to normal skin, and disease severity is significantly correlated with levels of IL-17 and TNF- α in blood. There is also a strong correlation between PASI scores and pathways related to IL-17 [44]. All the evidence suggests that IL-17 is the central effector cytokine in psoriasis.

3. Clinical proof of concept of targeting the IL-23/IL-17 axis for the treatment of plaque psoriasis

Table 1 summarizes biologics approved by the US Food and Drug Administration (FDA) for the systemic treatment of plaque psoriasis [45–48]. These biologics specifically target cytokines and the receptors involved in psoriasis pathogenesis. Treatment with biologics results in a greater efficacy and better safety profile compared to conventional systemic agents that do not target specific components of the immune system, and demonstrates the essential role of the IL-23/IL-17 axis in psoriasis [49, 50].

The first-generation anti-psoriatic biologics targeting cytokines focussed on TNF, an inflammatory cytokine implicated in psoriasis pathogenesis for a long time. High levels of TNF and its receptors (TNFR1 and TNFR2) are expressed in psoriatic lesional skin [51]. Four TNF blockers were approved by the FDA for psoriasis treatment (**Table 1**). TNF inhibition showed good therapeutic efficacy. At week 24, about 50 to 80 percent of patients reached 75% improvement in the psoriasis area and severity index (PASI75), and 10 to 20 percent got PASI100, which means 100% improvement [14]. Infliximab is the most efficacious TNF blocker followed by adalimumab and etanercept [50]. The primary mechanism of action of TNF blockers in improvement of psoriasis treatment is most likely due to its indirect effect on IL-23/IL-17 signaling pathway. The therapeutic effects of TNF blockade are observed to be associated with a strong reduction of IL-17-dependent genes [52]. In addition, TNF induces IL-23 expression in keratinocytes [53]. The exact roles of TNF in the pathogenesis of psoriasis are not yet completely understood.

Nevertheless, TNF is a versatile cytokine that not only involves inflammatory immune responses, but also contributes to cell death, cell cycling and tissue remodeling [54]. TNF blockers are well-known associated risk factors of serious infections,

Drug Class	Target molecule	Therapeutic Agent (Trade name)	Year of FDA approval	Dose and Administration	Other Indications
TNF blocker (biologics)	TNF	Etanercept (Enbrel®)	2004	50 mg twice weekly for 3 months, followed by 50 mg once weekly; S.C. injection	RA; JIA; PsA; AS
		Infliximab (Remicade®)	2006	5 mg/kg at weeks 0, 2, 6 followed by 5 mg/kg every 8 weeks; I.V. infusion	RA; PsA; AS; CD; UC
		Adalimumab (Humira®)	2008	80 mg on day 1 followed by 40 mg every other week; S.C. injection	RA; JIA; PsA; AS; CD; UC; HS; Uveitis
		Certolizumab pegol (Cimzia®)	2018	400 mg every other week; S.C. injection	RA; PsA; AS; CD; non-radio-graphic AS
IL-12/23 antagonist (biologics)	IL-12/23 p40	Ustekinumab (Stelara®)	2009	45 mg or 90 mg at weeks 0, 4, followed by 45 mg or 90 mg every 12 weeks; S.C. injection	PsA; CD; UC
IL-17 antagonist (biologics)	IL-17A	Secukinumab (Cosentyx®)	2015	300 mg at weeks 0, 1, 2, 3, 4, followed by 300 mg every 4 weeks; S.C. injection	PsA; AS; non-radio-graphic AS
		Ixekizumab (Taltz®)	2016	160 mg at week 0; 80 mg every 2 weeks for 3 months, followed by 80 mg every 4 weeks; S.C. injection	PsA; AS; non-radiographic AS
	IL-17RA	Brodalumab (Siliq®-US; Kyntheum®-Europe)	2017	210 mg at weeks 0, 1, 2, followed by 210 mg every 2 weeks; S.C. injection	none
IL-23 antagonist (biologics)	IL-23 p19	Guselkumab (Tremfya®)	2017	100 mg at weeks 0, 4, followed by 100 mg every 8 weeks; S.C. injection	PsA
		Tildrakizumab (Ilumya™)	2018	100 mg at weeks 0, 4, followed by 100 mg every 12 weeks; S.C. injection	none
		Risankizumab (Skyrizi™)	2019	150 mg at weeks 0, 4, followed by 150 mg every 12 weeks; S.C. injection	none

TNF = tumor necrosis factor; IL = interleukin; S.C. = subcutaneous; I.V. = intravenous; RA = rheumatoid arthritis; JIA = juvenile idiopathic arthritis; PsA = psoriatic arthritis; AS = ankylosing spondylitis; CD = crohn's disease; UC = ulcerative colitis; HS = hidradenitis suppurativa.

Table 1.
FDA approved biologics for systemic treatment of moderate-to-severe plaque psoriasis.

such as lower respiratory tract and skin and soft tissue infections like pneumonia and cellulitis [55]. After initial treatment of around 2 weeks, 2% ~ 5% of the patients developed paradoxical psoriasis: new lesions developed or the existing lesions got worse [54]. This side effect also happened when TNF blockers were used to treat other autoimmune diseases, including Crohn's disease and rheumatoid arthritis [53, 56]. It has been reported that IL-17A expression was strong in skin lesions from patients who had paradoxical psoriasis and needed other therapy [57]. This suggests that under some conditions, IL-17 is not down-regulated while blocking TNF α so that skin lesions continue to develop.

After TNF blockers, biologics that directly target the IL-23/IL-17 axis have been developed. The second-generation monoclonal antibody, ustekinumab, is targeting the subunit p40 common to IL-12 and IL-23, blocking signaling of their cognate receptors that induce a nonspecific inhibition of TH1 and TH17 [58, 59]. Ustekinumab has efficacy similar to TNF α inhibitors. It is better than etanercept, but not as good as infliximab. Ustekinumab received FDA approval for the treatment of moderate-to-severe psoriasis in 2009 (**Table 1**).

IL-17 is a central proinflammatory effector cytokine downstream of IL-23 and implicated in the pathogenesis of psoriasis. The third-generation monoclonal antibodies that neutralize IL-17 became available for the treatment of psoriasis (**Table 1**). Secukinumab and ixekizumab are human monoclonal antibodies against IL-17A. Brodalumab is blocking IL-17RA, which is the receptor for IL-17A, IL-17C, IL-17E, IL-17F and IL-17 A/F heterodimers. As IL-17A, IL-17C and IL-17F are all up-regulated in psoriatic skin [31], it is likely that brodalumab would have a better effect. In a study that brodalumab was given to patients who experienced unsuccessful treatment with either secukinumab or ixekizumab, PASI75, PASI90 and PASI100 scores were achieved in 69%, 44% and 28% of patients [60]. In phase III trials, 30–60% of patients treated with IL-17 antagonists reached PASI100 [61–65]. The superior efficacy of IL-17 blockade over neutralizing IL-12/IL23 and blocking TNF has been demonstrated in head-to-head clinical trials of brodalumab versus ustekinumab [62] and ixekizumab versus etanercept [61, 62].

The most common adverse effects of IL-17 antagonists are nasopharyngitis, upper respiratory tract infections, mucocutaneous candidiasis, transient neutropenia and injection site reactions. Mucocutaneous candidiasis observed by IL-17 inhibition or inborn genetic errors of IL-17 gene [66] suggests the innate, protective role of IL-17 against microbial pathogens on the skin. There is a black box warning for brodalumab due to the results from AMAGINE 1 and 2, where four patients committed suicide during the treatment period [64, 65].

IL-23 is known as the master regulator of TH17 cells. A fourth-generation of monoclonal antibodies against p19 subunits of IL-23, guselkumab, tildrakizumab and risankizumab, have been approved for treatment of moderate-to-severe psoriasis (**Table 1**). In contrast to ustekinumab, these biologics target IL-23 by neutralizing the p19 subunit without disrupting the IL-12 signaling pathway. Selectively targeting IL-23p19 provides better efficacy than ustekinumab [50]. IL-23 antagonists can reach a PASI90 in more than 50% of patients, confirming the pivotal role of IL-23 in the pathogenesis of psoriasis [67–69].

The head-to-head trial of guselkumab versus ustekinumab demonstrates superiority of selectively targeting p19 subunit of IL-23 among patients who had an inadequate response to ustekinumab with similar types of safety profiles [70]. As demonstrated by clinical trial outcomes, double blockade of IL-12 and IL-23 with ustekinumab resulted in lesser disease improvement versus single blockade of IL-23, confirming IL-23, but not IL-12, is a major player in psoriasis.

In addition, IL-23p19 antagonists exhibit significantly higher efficacy compared to all tested TNF blockers while maintaining a favorable safety profile [69, 71]. For example, guselkumab was superior ($p < 0.001$) to adalimumab for PASI90 response at week 48 (76.3% versus 47.9%), respectively. Compared with IL-17 antagonists, guselkumab exhibits a longer duration of therapeutic effect in patients with psoriasis [69]. This is probably because IL-23 is a key driver of TH17 cell differentiation and survival, and an upstream regulator of IL-17A. IL-17 producing cells are dependent on IL-23 for survival. IL-23 stimulates production of not only IL-17, but also other TH17 cytokines (for example, IL-22) by other immune cell types, including $\gamma\delta$ T cells.

The most common adverse events with the use of guselkumab and tildrakizumab are nasopharyngitis, upper respiratory tract infections, and headaches [67–69]. In contrast to IL-17 antagonists, the rate of mucocutaneous candidiasis was infrequent and comparable to healthy control subjects.

In conclusion, clinical outcomes of these biologics targeting IL-23p19 and IL17 are a strong argument for the IL-23/IL-17 axis in driving disease pathology. These molecular targeted therapies not only remarkably alleviate symptoms but also provide a deep understanding of the molecular mechanism of psoriatic disease.

4. New targeted therapeutics in development for topical treatment of psoriasis

Targeting a spectrum of inflammatory mediators involved in the pathogenesis of psoriasis will ensure a favorable safety profile and limited side effects. As discussed above, biological treatment, along with evolving systemic therapy, has revolutionized severe psoriasis management. Development of new and effective biologics has made much progress in our understanding of psoriasis immunopathology. Topical therapy implies good compliance for the psoriatic patients, few adverse systemic reactions as compared to systemic medications. However, biologics targeting proinflammatory cytokines are not suitable for topical route delivery due to the large size and poor permeability into skin. Small molecules targeting intracellular signaling pathway have some advantages over biologic agents, particularly the possibility of topical administration, lack of immunogenicity, the simplified synthesis processes, low-cost production, placing these drugs in a very attractive position for future drug discovery and development in topical treatment of psoriasis. New topical targeted therapeutics undergoing efficacy and safety studies are summarized in **Table 2** based on the information available from the website of ClinicalTrials.gov [72].

4.1 ROR γ antagonists

ROR γ t is a master transcription factor of TH17 cells, which activates the transcription of IL-23 receptor gene as well as pro-inflammatory cytokines such as IL-17A, IL-17F, IL-21, and IL-22, and enhances the inflammatory process. Clinical success of biologics in the IL23/IL17 axis suggests that inhibiting ROR γ could be an effective alternative therapy for psoriasis.

Vitae Pharmaceuticals (acquired by Allergan, later by Abbvie) developed an orally active ROR γ t antagonist VTP-43742 for the treatment of autoimmune diseases, including psoriasis through suppression of IL-17A production and down-regulation of the IL-23 receptor [73]. VTP-43742 with high systemic exposure demonstrated a clear signal of efficacy over a short four-week period from a Phase 2a clinical trial

Drug Class	Target molecule	Agent/company	Administration	Highest clinical trial stage	Status
ROR γ antagonist (small molecule)	ROR γ	GSK2981278 / Glaxosmithkline	Topical	Phase 1/2	Completed (May 2017)
		ESR-114 /Escalier Biosciences B.V.	Topical	Phase 1/2	Completed (June 2019)
JAK inhibitor (small molecule)	pan-JAKs	Tofacitinib (CP-690550)/Pfizer	Topical	Phase 2	Completed (Jul 2009) (Nov 2011) (Sept 2014)
	JAK1/2	Ruxolitinib (Opzelura™)/Incyte	Topical	Phase 2	Completed (Apr 2009) (Apr 2009) (May 2009)
		CT327/Creabilis SA	Topical	Phase 2	Completed (Jan 2011) (Sept 2012)
	TYK2/JAK1	PF-06700841/Pfizer	Topical	Phase 2	Completed (Apr 20, 2021)
DNMT Inhibitor (small molecule)	DNMTs	DUR-928/Durect	Topical	Phase 2	Completed (May 20, 2020)
PDE4 inhibitor (small molecule)	PDE4	AN-2728 (crisaborole)/Pfizer	Topical	Phase 2	Completed (Mar 2008) (Dec 2008) (June 2010) (June 2011)
		ARQ-151 (roflumilast)/Arcutis Biotherapeutics, Inc.	Topical	Phase 3	Completed (Nov 2020) (Est. Dec 2022)
AhR agonist (small molecule)	AhR	GSK2894512 (Tapinarof, WBI-1001)/Glaxosmithkline	Topical	Phase 3	Withdrawn (Sept 2018) (The decision is a business decision based on the need to prioritize and focus resources within GSK)
		Tapinarof (WBI-1001, GSK2894512, DMVT-505)/Dermavant Sciences	Topical	Phase 3	Completed (May 2020); FDA acceptance of NDA for Tapinarof in plaque psoriasis

DNMT = DNA methyltransferase; PDE4 = phosphodiesterase-4; AhR = aryl hydrocarbon receptor.

Table 2.
New targeted therapeutics under clinical trials for topical treatment of plaque psoriasis.

in psoriatic patients [74]. It provides a proof of concept of ROR γ antagonists for the treatment of psoriasis, consistent with the clinical success of biologics in the IL23/IL17 axis.

Nevertheless, two drug candidates terminated their clinical trials due to potential safety liability. Four patients in the 700 mg VTP-43742 dose group showed reversible transaminase elevations, which led the company to terminate the development of VTP-43742. In addition, Takeda Pharmaceutical Company terminated a phase 1 trial of oral ROR γ antagonist TAK828 for evaluation of the safety, tolerability, pharmacokinetics, and pharmacodynamics of escalating multiple doses in healthy volunteers in the United states (NCT02817516). The decision was based on critical non-monitorable toxicology findings in both monkeys and rats, combined with the potential for teratogenicity in humans [75].

ROR γ has two isoforms, ROR γ 1 and ROR γ 2 (most commonly referred to as ROR γ t) [76]. ROR γ t is a differentially spliced isoform of ROR γ 1, 19 amino acids shorter at N-terminus. The biochemical assay for evaluation of the compounds using LBD of the receptor will result in pan-ROR γ antagonists. ROR γ t is exclusively expressed in a few distinct cell types of the immune system, including Th17, Tc17, $\gamma\delta$ T cells and regulatory T cells [43, 77–80] whereas, ROR γ 1 exhibits oscillatory expression in liver, brown adipose tissue, and kidney [76, 81]. Systemic exposure of the Pan-ROR γ antagonists may have off-target effects against the not-intended target, ROR γ 1, during the treatment of the diseases. In addition, a mouse genetics study indicated that 50% of embryonic ROR γ deficient mice developed T-cell lymphoma [82]. Lymphoma was also observed in adult ROR γ knockout mice with immune systems intact [83]. The phenotypes of ROR γ knockout mice cause concerns of the consequences of systemic treatment of ROR γ antagonists in the patients with psoriasis.

Developing ROR γ antagonists with the skin-restricted exposure may alleviate the safety risk of systemic exposure while still maintaining similar efficacy as biologics in the IL-23/IL17 pathway, and may provide a new option as topical targeted therapeutics for psoriasis patients. Phase 1 trial of topical ROR γ antagonist GSK2981278 for the treatment of psoriasis was not advanced further (**Table 2**) [84]. 0.03%, 0.1%, 0.8% and 4% GSK2981278 ointments were used in the trial, respectively. Across all doses, infiltrate thickness was not altered. Biomarker results did not support that the target was engaged. Although GSK2981278 was shown *in vitro* as a highly potent and selective antagonist of ROR γ , the limited *in vivo* efficacy in reduction of epidermal thickness (23% reduction vs. placebo with imiquimod (IMQ) control at 1% GSK2981278 ointment) was observed in IMQ-induced mouse psoriasis-like inflammation model [85]. The skin exposure of GSK2981278 was not disclosed while its systemic exposure in mouse serum was relatively low [85]. It is speculated that insufficient drug exposure at the target site might be one of the reasons for its lacking efficacy in phase 1 trial [84].

More effort was then focused on developing ROR γ antagonists in restricted exposure and prolonged action at the skin while being rapidly eliminated from the systemic circulation for topical therapy in psoriasis. ESR114 topical gel is a selective, potent inhibitor of ROR γ designed to have its pharmacological activity targeted to the skin with minimal systemic absorption [86]. In 2019, Escalier Biosciences completed a phase I/II trial evaluating ESR-114 topical gel in patients with mild-to-moderate psoriasis in USA and Canada (NCT03630939, **Table 2**). Nevertheless, no trial results were disclosed yet. In addition, it was reported that a novel series of benzimidazole with ROR γ antagonistic activity, SHR168442, was developed with desirable skin-restricted PK properties for a topical drug [87]. SHR168442 suppressed the IL-17 gene transcription, and reduced IL-17 cytokine secretion, and, more importantly, achieved skin-restricted exposure suitable for topical delivery. In the IMQ-induced and IL-23-induced psoriasis-like skin inflammation mouse models, SHR168442 ointment

exhibited excellent efficacy, which correlated with the reduction of Th17 pathway cytokines, IL-17A, IL-6 and TNF α . This novel ROR γ antagonist may represent a new option as topical targeted therapeutics for mild to moderate psoriasis patients. Results from further clinical evaluation of this specific mechanism for the treatment of mild to moderate psoriasis are highly anticipated.

4.2 JAK inhibitors

The Janus kinase–signal transducer and activator of transcription (JAK–STAT) pathway plays a crucial role in intracellular signaling of cytokine of many cellular processes, important in both normal and pathological states of immune-mediated inflammatory diseases [88]. There are four different types of JAK proteins: JAK1, JAK2, JAK3 and TYK2. The IL-23 receptor relies on a heterodimer of JAK2 and TYK2 for signal transduction, thus highlighting the role of JAKs in the pathogenesis of psoriasis and the therapeutic potential of JAK inhibitors in psoriasis. TYK2-deficient mice, as compared to wild-type mice, exhibit significantly reduced ear swelling and less epidermal hyperplasia when injected with IL-23 [89, 90]. In the absence of TYK2, the production of IL-17 and IL-22 and skin infiltration of various immune cells were also impaired. Taken together with the clinical success of biologics blocking either IL-23 or IL-17 signaling (**Table 1**), these results suggest the great potential for JAK inhibitors and, especially, for TYK2 inhibitors in the treatment of psoriasis.

JAK inhibitors are already on the market for rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis [24]. JAK inhibitors have been tested as potential treatments for psoriasis. The first generation of JAK inhibitors target multiple members of the JAK family and thus display a broader effect but also present more side effects. Many JAK inhibitors tested for oral treatment of psoriasis have only been examined in phase II trials except tofacitinib (reached phase III). It is doubtful that they will be tested further. In recent years, selective TYK2 inhibitors have been developed, and several phase III trials are in progress. The highly selective TYK2 inhibitor BMS-986165 has shown high efficacy toward psoriasis, confirming the important role of the IL-23/IL-17 axis in pathogenesis of psoriasis [91]. Several JAK inhibitors with different selectivity spectrums are under clinical development for the topical treatment of psoriasis (**Table 2**).

Tofacitinib (pan-JAK inhibitor) has been approved for the treatment of psoriatic arthritis, but not of psoriasis. Oral tofacitinib has been tested in phase III for psoriasis. Although tofacitinib shows a favorable clinical effect on plaque psoriasis symptoms, herpes zoster occurs during tofacitinib treatment, especially in Asian populations including the Japanese [48]. In phase 2b trial, the ointment formulation of tofacitinib was found to have no considerable effect at week 12 in comparison to that of the vehicle [92].

Ruxolitinib is a selective JAK1 and JAK2 inhibitor that inhibits various cytokines involved in the signaling of TH1 and TH17 pathways, including IL-12, IL-23 and IFN γ , which are associated with psoriasis. Its cream formulation has been approved by FDA for the treatment of atopic dermatitis, but not of psoriasis [93]. In phase II studies, ruxolitinib was studied as a topical ointment for mild-to-moderate psoriasis (**Table 2**). In an open phase 2 study conducted with 28 patients, a greater reduction in lesion severity score was observed for topical ruxolitinib as compared with vehicle and with calcipotriene [94]. The systemic absorption of the product was minimal. In a subsequent phase IIb, double-blind, randomized, vehicle-controlled study, 200 patients with mild-to-moderate chronic plaque psoriasis were treated with topical ruxolitinib for 3 months and the results

indicated the mean PASI improvement was 40% compared with placebo [95]. Both studies reported the main adverse event was local irritation, which was more frequent in patients treated with placebo. To date, no phase III study of ruxolitinib in psoriasis has begun yet.

PF-06700841 is a potent dual inhibitor of TYK2 and JAK1, which was shown to be safe and well tolerated in the oral treatment at doses up to 200 mg once daily in a phase I clinical trial [96]. No other clinical trials with oral PF-06700841 in psoriasis are now ongoing. A phase IIb study of topical application of PF-06700841 cream involving patients with mild-to-moderate psoriasis (NCT03850483) was recently completed (April 20, 2021). The trial results are not yet available.

4.3 DNMT inhibitors

DUR-928 is an endogenous sulfated oxysterol that acts as an epigenetic regulator [97]. It binds to and inhibits the activity of DNMTs, DNMT-1, 3a and 3b, inhibiting DNA methylation, and thereby modulating the expression of the genes associated with stress response, lipid biosynthesis and cell death. Improvement of cell survival and reduction of lipotoxicity and inflammation by DUR-928 were observed in animal models and from DURECT's clinical trials in alcohol-associated hepatitis (AH) and nonalcoholic steatohepatitis (NASH). The rationale of topical application of DUR-928 in psoriasis is not clear. A phase IIb study of topical application of DUR-928 topical solution in patients with mild-to-moderate psoriasis (NCT03837743) was completed on August 20, 2020 (**Table 2**). The trial results are not yet disclosed.

4.4 PDE4 inhibitors

The oral phosphodiesterase-4 (PDE4) inhibitor apremilast was approved for the treatment of moderate to severe plaque psoriasis [98]. However, apremilast has only modest efficacy with PASI75 rates clearly lower than biologics. Inhibition of PDE4 indirectly down regulates immune modulators, including TNF α , IFN γ , IL-17 and IL-23 [99]. Due to the potential adverse events associated with oral administration, the topical PDE4 inhibitors, crisaborole and roflumilast, are being investigated as an alternative treatment of psoriasis aiming to avoid systemic adverse effects (**Table 2**).

AN-2728 (crisaborole) ointment has been approved for the treatment of atopic dermatitis [100]. AN-2728 is a newer generation of PDE4 inhibitors [101]. Its binding mode to the catalytic site of PDE4 is distinct from traditional PDE4 inhibitors and can reduce pro-inflammatory cytokines TNF α , IL-2, IFN γ , and IL-5. In phase 2 studies to treat mild-to-moderate plaque-type psoriasis, AN-2728 ointment showed modest efficacy (40% of patients achieved a ≥ 2 grade improvement as assessed by the overall target Plaque Severity Score) [102]. Most adverse effects were mild to moderate.

The oral PDE4 inhibitor roflumilast has been approved by FDA for the treatment of chronic obstructive pulmonary disease (COPD) exacerbation since 2011 [103]. The topical roflumilast, in a high-water-content moisturizing cream base vehicle containing the cosmetic solvent ethoxydiglycol, is being investigated for the treatment of plaque psoriasis [104]. Its inhibitor affinity (IC₅₀ values) is 25 to 300 folds more potent than either apremilast or crisaborole depending on PDE4 isoform analyzed [105]. In the phase 2b trial, approximately 85% of the enrolled patients had moderate-to-severe psoriasis and a generally similar percentage of patients in the roflumilast 0.3% group (31%) met the criterion for the PASI75 response at week 8 although differences in trial design do not allow to make direct comparisons [104, 105].

Oral apremilast has been associated with gastrointestinal adverse events of diarrhea and nausea, whereas topical roflumilast cream was associated with less than 1% of each of these events in this phase 2b trial. This may be a result of topical administration bypassing the gastrointestinal tract. Longer and larger trials are in progress to determine the durability and safety of roflumilast in psoriasis (**Table 2**).

4.5 AhR agonists

Tapinarof (also known as WBI-1001, GSK2894512, DMVT-505) is a naturally derived small molecule produced by bacterial symbionts of entomopathogenic nematodes [106]. Broad cellular profiling of tapinarof identified aryl hydrocarbon receptor (AhR) as a primary target [107]. Tapinarof activates the AhR pathway through direct binding. It was reported that AhR activation can modify transcriptional regulation of the immune system and, specifically, affect the differentiation of Th17 and Treg cells [108]. Tapinarof has been shown to inhibit IL-17A message expression by approximately 50% and robustly increase IL-22 levels [107]. Furthermore, 1% tapinarof cream can reduce imiquimod (IMQ)-induced skin inflammation and suppress IMQ-induced IL-17A and IL-17F gene expression in AhR-sufficient, but not AhR-deficient mice.

Topical 1.0% tapinarof met its primary endpoint in patients with mild-to-moderate psoriasis from a randomized double-blind placebo-controlled phase II trial [109]. The improvement in PGA at week 12 was 62.8% for patients randomized to tapinarof when compared with 13.0% for patients randomized to placebo ($p < 0.0001$). The adverse events observed in patients treated with tapinarof were all mild to moderate in intensity.

In 2018, GlaxoSmithKline (GSK) withdrew its phase III trial of tapinarof (GSK2894512) and sold mostly global rights of its Phase III-bound psoriasis candidate tapinarof to Dermavant Sciences [110]. On 9/30/2021, Dermavant Sciences disclosed final results from Phase III PSOARING 3 long-term extension study of tapinarof, a 1.0% once a daily, in patients with plaque psoriasis [111]. 58.2% (302/519) of patients with a PGA score ≥ 2 achieved a PGA score of 0 or 1. Moreover, 40.9% (312/763) of all patients achieved complete disease clearance (PGA score of 0). Those results demonstrate tapinarof's continued improvement in efficacy beyond the 12-week pivotal studies. Treatment-emergent adverse events (TEAEs) were mostly mild to moderate, at application sites, and associated with a low discontinuation rate (5.4%). Incidence and severity of folliculitis and contact dermatitis remained stable with long-term use (up to 52 weeks) and were associated with low discontinuation rates (1.2% and 1.4%, respectively). The FDA accepted the New Drug Application submitted in May 2021, and assigned a Prescription Drug User Fee Act target action date in the second quarter of 2022.

5. Conclusion

A rapidly growing body of literature suggests that the IL-23/IL-17 axis is the major pathway that drives the chronic inflammation underlying psoriasis pathophysiology. The recent years have witnessed that superior clinical efficacy of IL-23/IL-17 pathway biologics in the systemic treatment of psoriasis brings to a major paradigm shift for the management of moderate-to-severe psoriasis. Nevertheless, lack of molecular targeted therapies remains for topical treatment of psoriasis.

With the rapid development of small molecule drugs for the topical treatment of psoriasis, molecular targeted therapies in the IL-23/IL17 axis have the potential to ascertain their role as effective and safe therapy. Although tapinarof and roflumilast are promising therapies in topical treatment of psoriasis, there are still considerable challenges in topical treatment. Many other topical therapeutic agents hold promise and warrant further investigation. Limitations of this chapter include a paucity of randomized controlled clinical trials for topical agents in the treatment of psoriasis, especially for most agents with none or only preliminary data available. Some studies report on a limited duration and a limited number of participants challenging generalizability to the clinic population. Much work is still required for the next breakthrough in the discovery of novel effective and safe topical therapy for psoriasis.

Author details

Suxing Liu^{1*}, Di Li¹ and Weikang Tao²

1 Eternity Bioscience Inc., Cranbury, NJ, USA

2 Shanghai Hengrui Pharmaceutical Co. Ltd., Shanghai, China

*Address all correspondence to: lius@eternitybioscience.com

IntechOpen

© 2022 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

- [1] Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. *Lancet*. 2007;**370**:263-271. DOI: 10.1016/S0140-6736(07)61128-3
- [2] Parisi R, Iskandar IYK, Kontopantelis E, Sugustin M, Griffiths CEM, Ashcroft D. On behalf of the global psoriasis atlas. National, regional, and worldwide epidemiology of psoriasis: Systematic analysis and modeling study. *BMJ*. 2020;**369**:m1590. DOI: 10.1136/bmj.m1590
- [3] Danielsen K, Duvetorp A, Iversen L, Ostergaard M, Seifert O, Tveit KS, et al. Prevalence of psoriasis and psoriatic arthritis and patient perceptions of severity in Sweden, Norway and Denmark: Results from the nordic patient survey of psoriasis and psoriatic arthritis. *Acta Dermato-Venereologica*. 2019;**99** (1-2):18-25. DOI: 10.2340/00015555-3017
- [4] Menter A, Korman NJ, Elmetts CA, Feldman SR, Gelfand JM, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. *Journal of the American Academy of Dermatology*. 2009;**60**(4):643-659. DOI: 10.1016/j.jaad.2008.12.032
- [5] van de Kerkhof PC, Reich K, Kavanaugh A, bachelez H, Barker J, Girolomoni G, et al. Physician perspectives in the management of psoriasis and psoriatic arthritis: Results from the population-based multinational assessment of psoriasis and psoriatic arthritis survey. *Journal of the European Academy of Dermatology and Venereology*. 2015;**29**(10):2002-2010. DOI: 10.1111/jdv.13150
- [6] Boehncke WH, Schon MP. Psoriasis. *Lancet*. 2015;**386**(9997):983-994. DOI: 10.1016/S0140-6736(14)61909-7
- [7] Mason AR, Mason J, Cork M, Dooley G, Hancock H. Topical treatments for chronic plaque psoriasis. *Cochrane Database of Systematic Reviews*. 2013;**28**(3):CD005028. DOI: 10.1002/14651858.CD005028.pub3
- [8] Schlager JG, Rosumeck S, Werner RN, Jacobs A, Schmitt J, Schlager C, et al. Topical treatments for scalp psoriasis. *Cochrane Database of Systematic Reviews*. 2016;**26**(2):CD009687. DOI: 10.1002/14651858.CD009687.pub2
- [9] Maul JT, Anzengruber F, Conrad C, Cozzio A, Hausermann P, Jalili A, et al. Topical treatment of psoriasis vulgaris: The Swiss treatment pathway. *Dermatology*. 2021;**237**(2):166-178
- [10] Coondoo A, Phiske M, Verma S, Lahiri K. Side-effects of topical steroids: A long overdue revisit. *Indian Dermatology Online Journal*. 2014;**5**(4):416-425. DOI: 10.4103/2229-5178.142483
- [11] Oda DC, de Korte J, Sprangers MAG, de Rie M, Smets EMA. Satisfaction with treatment among patients with psoriasis: A web-based survey study. *The British Journal of Dermatology*. 2013;**169**(2):398-405. DOI: 10.1111/bjd.12372
- [12] Blauvelt A. T-helper 17 cells in psoriatic plaques and additional genetic links between IL-23 and psoriasis. *The Journal of Investigative Dermatology*. 2008;**128**:1064-1067. DOI: 10.1038/jid.2008.85
- [13] Fitch E, Harper E, Skorcheva I, Kurtz SE, Blauvelt. Pathophysiology of psoriasis: Recent advances on IL-23 and

- Th17 cytokines. *Current Rheumatology Reports*. 2007;**9**:461-467. DOI: 10.1007/s11926-007-0075-1
- [14] Hawkes JE, Yan BY, Chan TC, Krueger JG. Discovery of the IL-23/IL-17 Signaling pathway and the treatment of psoriasis. *Journal of Immunology*. 2018;**201**(6):1605-1613. DOI: 10.4049/jimmunol.1800013
- [15] Uyemura K, Yamamura M, Fivenson DF, Modlin RL, Nickoloff BJ. The cytokine network in lesional and lesion-free psoriatic skin is characterized by a T-helper type I cell-mediated response. *The Journal of Investigative Dermatology*. 1993;**101**:701-705. DOI: 10.1111/1523-1747.ep12371679
- [16] Chodorowska G. Plasma concentrations of IFN-gamma and TNF-alpha in psoriatic patients before and after local treatment with dithranol ointment. *Journal of the European Academy of Dermatology and Venereology*. 1998;**10**:147-151. DOI: 10.1111/j.1468-3083.1998.tb00715.x
- [17] Harden JLLM, Johnson-Huang MF, Chamian E, Lee T, Pearce CL, Leonardi A, et al. Humanized anti-IFN- γ (HuZAF) in the treatment of psoriasis. *The Journal of Allergy and Clinical Immunology*. 2015;**135**:553-556. DOI: 10.1016/j.jaci.2014.05.046
- [18] Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Pukka M, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. *Nature*. 2006;**441**(7090):235-238. DOI: 10.1038/nature04753
- [19] Korn T, Bettelli E, Gao W, Awasthi A, Jager A, Strom TB, et al. IL-21 initiates an alternative pathway to induce proinflammatory T(H)17 cells. *Nature*. 2007;**448**(7152):484-487. DOI: 10.1038/nature05970
- [20] Yang L, Anderson DE, Baecher-Allan C, Hastings WD, Bettelli E, Pukka M, et al. IL-21 and TGF-beta are required for differentiation of human T(H)17 cells. *Nature*. 2008;**454**(7202):350-352. DOI: 10.1038/nature07021
- [21] Cua DJ, Sherlock J, Chen Y, Murphy CA, Joyce B, Seymour B, et al. Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. *Nature*. 2003;**421**(6924):744-748. DOI: 10.1038/nature01355
- [22] Langrish CL, Chen Y, Blumenschein WM, Mattson J, Basham B, Sedgwick JD, et al. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. *The Journal of Experimental Medicine*. 2005;**201**(2):233-240. DOI: 10.1084/jem.20041257
- [23] Chen Z, Laurence A, Kanno Y, Pacher-Zavisin M, Zhu B-M, Tato C, et al. Selective regulatory function of Socs3 in the formation of IL-17-secreting T cells. *Proceedings of the National Academy of Sciences of the United States of America*. 2006;**103**(21):8137-8142. DOI: 10.1073/pnas.0600666103
- [24] Kvist-Hansen A, Hansen PR, Skov L. Systemic treatment of psoriasis with JAK inhibitors: A review. *Dermatology and Therapy*. 2020;**10**(1):29-42. DOI: 10.1007/s13555-019-00347-w
- [25] Li AG, Wang D, Feng XH, Wang XJ. Latent TGFbeta1 overexpression in keratinocytes results in a severe psoriasis-like skin disorder. *The EMBO Journal*. 2004;**23**:1770-1791. DOI: 10.1038/sj.emboj.7600183

- [26] Sano S, Chan KS, Carbajal S, Clifford J, Peavey M, Kiguchi K, et al. Stat3 links activated keratinocytes and immunocytes required for development of psoriasis in a novel transgenic mouse model. *Nature Medicine*. 2005;**11**:43-49. DOI: 10.1038/nm1162
- [27] Stockinger B, Veldhoen M. Differentiation and function of Th17 T cells. *Current Opinion in Immunology*. 2007;**19**(3):281-286. DOI: 10.1016/j.coi.2007.04.005
- [28] Oppmann B, Lesley R, Blom B, Timans JC, Xu Y, Hunte B, et al. Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. *Immunity*. 2000;**13**(5):715-725. DOI: 10.1016/s1074-7613(00)00070-4
- [29] Piskin G, Sylva-Steenland RM, Bos JD, Teunissen MB. In vitro and in situ expression of IL-23 by keratinocytes in healthy skin and psoriasis lesions: Enhanced expression in psoriatic skin. *Journal of Immunology*. 2006;**176**(3):1908-1915. DOI: 10.4049/jimmunol.176.3.1908
- [30] Res PC, Piskin G, de Boer OJ, van der Loos CM, Teeling P, Bos JD, et al. Overrepresentation of IL-17A and IL-22 producing CD8 T cells in lesional skin suggests their involvement in the pathogenesis of psoriasis. *PLoS One*. 2010;**5**(11):e14108. DOI: 10.1371/journal.pone.0014108
- [31] Johansen C, Usher PA, Kjellerup RB, Lundsgaard D, Iversen L, Kragballe K. Characterization of the interleukin-17 isoforms and receptors in lesional psoriatic skin. *The British Journal of Dermatology*. 2009;**160**(2):319-324. DOI: 10.1111/j.1365-2133.2008.08902.x
- [32] Nair RP, Duffin KC, Helms C, Ding J, Stuart PE, Goldgar D, et al. Genome-wide scan reveals association of psoriasis with IL-23 and NF-kappaB pathways. *Nature Genetics*. 2009;**41**(2):199-204. DOI: 10.1038/ng.311
- [33] Cargill M, Schrodi SJ, Chang M, Garcia VE, Brandon R, Callus KP, et al. A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. *American Journal of Human Genetics*. 2007;**80**(2):273-290. DOI: 10.1086/511051
- [34] Chan JR, Blumenschein W, Murphy E, Diveu C, Wiekowski M, Abbondanzo S, et al. IL-23 stimulates epidermal hyperplasia via TNF and IL-20R2-dependent mechanisms with implications for psoriasis pathogenesis. *The Journal of Experimental Medicine*. 2006;**203**:2577-2587. DOI: 10.1084/jem.20060244
- [35] van der Fits L, Mourits S, Voerman JSA, Kant M, Boon L, Laman JD, et al. Imiquimod-induced psoriasis-like skin inflammation in mice is mediated via the IL-23/IL-17 axis. *Journal of Immunology*. 2009;**182**(9):5836-5845. DOI: 10.4049/jimmunol.0802999
- [36] Lee E, Trepicchio WL, Oestreicher JL, Pittman D, Wang F, Chanian F, et al. Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. *The Journal of Experimental Medicine*. 2004;**199**:125-130. DOI: 10.1084/jem.20030451
- [37] Kulig P, Musiol S, Freiburger SN, Schreiner B, Gyulveszi G, Russo G, et al. IL-12 protects from psoriasiform skin inflammation. *Nature Communications*. 2016;**7**:13466. DOI: 10.1038/ncomms13466
- [38] Wiekowski MT, Leach MW, Evans EW, Sullivan L, Chen S-C,

- Vassileva G, et al. Ubiquitous transgenic expression of the IL-23 subunit p19 induces multiorgan inflammation, runting, infertility, and premature death. *Journal of Immunology*. 2001;**166**:7563-7570. DOI: 10.4049/jimmunol.166.12.7563
- [39] Kopp T, Lenz P, Bello-Fernandez C, Kastelein RA, Kupper TS, Sting G. IL-23 production by secretion of endogenous p19 and transgenic p40 in keratin 14/p40 transgenic mice: Evidence for enhanced cutaneous immunity. *Journal of Immunology*. 2003;**170**:5438-5444. DOI: 10.4049/jimmunol.170.11.5438
- [40] McGeachy MJ, Chen Y, Tato CM, Laurence A, Joyce-Shaikh B, Blumenschein WM, et al. The interleukin 23 receptor is essential for the terminal differentiation of interleukin 17-producing effector T helper cells in vivo. *Nature Immunology*. 2009;**10**(3):314-324. DOI: 10.1038/ni.1698
- [41] Cai Y, Shen X, Ding C, Qi C, Li K, Li X, et al. Pivotal role of dermal IL-17-producing $\gamma\delta$ T cells in skin inflammation. *Immunity*. 2011;**35**(4):596-610. DOI: 10.1016/j.immuni.2011.08.001
- [42] Muromoto R, Hirao T, Tawa K, Hirashima K, Kon S, Kital Y, et al. IL-17A plays a central role in the expression of psoriasis signature genes through the induction of I κ B- ζ in keratinocytes. *International Immunology*. 2016;**28**(9):443-452. DOI: 10.1093/intimm/dxw011
- [43] Ivanov II, McKenzie BS, Zhou L, Tadokoro CE, Lepelley A, Lafaille JJ, et al. The orphan nuclear receptor ROR γ t directs the differentiation program of proinflammatory IL-17+ T helper cells. *Cell*. 2006;**126**:1121-1133. DOI: 10.1016/j.cell.2006.07.035
- [44] Chiricozzi A, Suárez-Fariñas M, Fuentes-Duculan J, Cueto I, Li K, Tian S, et al. Increased expression of interleukin-17 pathway genes in nonlesional skin of moderate-to-severe psoriasis vulgaris. *The British Journal of Dermatology*. 2016;**174**(1):136-145. DOI: 10.1111/bjd.14034
- [45] Afonina IS, Nuffel EV, Beyaert R. Immune responses and therapeutic options in psoriasis. *Cellular and Molecular Life Sciences*. 2021;**78**(6):2709-2727. DOI: 10.1007/s00018-020-03726-1
- [46] Stewart J. New treatments for plaque psoriasis—latest FDA approvals. 2021. Available from: <https://www.drugs.com/medical-answers/new-drugs-treatment-plaque-psoriasis-3511670/> [Accessed: October 6, 2021]
- [47] Yang K, Oak ASW, Elewski BE. Use of IL-23 inhibitors for the treatment of plaque psoriasis and psoriatic arthritis: A comprehensive review. *The American Journal of Dermatopathology*. 2021;**22**:173-192. DOI: 10.1007/s40257-020-00578-0
- [48] Honma M, Hayashi K. Psoriasis: Recent progress in molecular-targeted therapies. *The Journal of Dermatology*. 2021;**48**(6):761-777. DOI: 10.1111/1346-8138.15727
- [49] Ronholt K, Iversen L. Old and new biological therapies for psoriasis. *International Journal of Molecular Sciences*. 2017;**18**(11):2297. DOI: 10.3390/ijms18112297
- [50] ten Bergen LL, Petrovic A, Aarebrot AK, Appel S. The TNF/IL-23/IL17 axis—head-to-head trials comparing different biologics in psoriasis treatment. *Scandinavian Journal of Immunology*. 2020;**92**:e12946. DOI: 10.1111/sji.12946

- [51] Ettehadi P, Greaves MW, Wallach D, Aderka D, Camp RDR. Elevated tumor necrosis factor-alpha (TNF- α) biological-activity in psoriatic skin-lesions. *Clinical and Experimental Immunology*. 1994;**96**:146-151. DOI: 10.1111/j.1365-2249.1994.tb06244.x
- [52] Zaba LC, Suarez-Farina M, Fuentes-Duculan J, Nograles KE, Guttman-Yassky E, Cardinale I, et al. Effective treatment of psoriasis with etanercept is linked to suppression of IL-17 signaling, not immediate response TNF genes. *The Journal of Allergy and Clinical Immunology*. 2009;**124**:1022-1030. DOI: 10.1016/j.jaci.2009.08.046
- [53] Li SJ, Perez-Chada LM, Merola JF. TNF inhibitor-induced psoriasis: Proposed algorithm for treatment and management. *Journal of Psoriasis and Psoriatic Arthritis*. 2019;**4**(2):70-80. DOI: 10.1177/2475530318810851
- [54] Banno T, Gazel A, Blumenberg M. Effects of tumor necrosis factor-alpha (TNF alpha) in epidermal keratinocytes revealed using global transcriptional profiling. *The Journal of Biological Chemistry*. 2004;**279**:32633-32642. DOI: 10.1074/jbc.M4006422000
- [55] Dommasch ED, Abuabara K, Shin DB, Nguyen J, Troxel AB, Gelfand JM. The risk of infection and malignancy with tumor necrosis factor antagonists in adults with psoriatic disease: A systematic review and meta-analysis of randomized controlled trials. *Journal of the American Academy of Dermatology*. 2011;**64**(6):1035-1050
- [56] Mazloom SE, Yan D, Hu JZ, Ya J, Husni ME, Warren CB, et al. TNF- α inhibitor-induced psoriasis: A decade of experience at the Cleveland Clinic. *Journal of the American Academy of Dermatology*. 2020;**83**(6):1590-1598. DOI: 10.1016/j.jaad.2018.12.018
- [57] Tillack C, Ehmann LM, Friedrich M, Laubender RP, Papay P, Vogelsang H, et al. Anti-TNF antibody-induced psoriasiform skin lesions in patients with inflammatory bowel disease are characterised by interferon- γ -expressing Th1 cells and IL-17A/IL-22-expressing Th17 cells and respond to anti-IL-12/IL-23 antibody treatment. *Gut*. 2014;**63**(4):567-577. DOI: 10.1136/gutjnl-2012-302853
- [58] Leonardi CL, Kimball AB, Papp KA, Yielding N, Guzzo C, Wang Y, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX I). *Lancet*. 2008;**37**(9624):1665-1674. DOI: 10.1016/S0140-6736(08)60725-4
- [59] Griffiths CE, Strober BE, van de Kerkhof P, Ho V, Fidelus-Gort R, Yielding N, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *The New England Journal of Medicine*. 2010;**362**(2):118-128. DOI: 10.1056/NEJMoa0810652
- [60] Kimmel G, Chima M, Kim HJ, Bares J, Yao CJ, Singer G, et al. Brodalumab in the treatment of moderate to severe psoriasis in patients when previous anti-interleukin 17A therapies have failed. *Journal of the American Academy of Dermatology*. 2019;**81**(3):857-859. DOI: 10.1016/j.jaad.2019.05.007
- [61] Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, et al. UNCOVER-3 study group. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *The New England Journal of Medicine*.

2016;**375**(4):345-356. DOI: 10.1056/NEJMoa1512711

[62] Griffiths CE, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, et al. UNCOVER-2 and UNCOVER-3 investigators. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): Results from two phase 3 randomised trials. *Lancet*. 2015;**386**:541-551. DOI: 10.1016/S0140-6736(15)60125-8

[63] Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, et al. FIXTURE study group. Secukinumab in plaque psoriasis—results of two phase 3 trials. *The New England Journal of Medicine*. 2014;**371**:326-338. DOI: 10.1056/NEJMoa1314258

[64] Lebwohl M, Strober B, Menter A, Gordon K, Weglowska J, Puig L. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. *The New England Journal of Medicine*. 2015;**373**:1318-1328. DOI: 10.1056/NEJMoa1503824

[65] Papp KA, Reich K, Paul C, Blauvelt A, Baran W, Bolduc C, et al. A prospective phase III, randomised, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. *The British Journal of Dermatology*. 2016;**175**(2):273-286. DOI: 10.1111/bjd.14493

[66] Peul A, Cypowyj S, Bustamante J, Wright JF, Liu L, Lim HK, et al. Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. *Science*. 2011;**332**:65-68. DOI: 10.1038/cti.2016.71

[67] Reich K, Armstrong AW, Foley P, Song M, Wasfi Y, Randazzo B, et al. Efficacy and safety of guselkumab, an

anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. *Journal of the American Academy of Dermatology*. 2017;**76**:418-431. DOI: 10.1016/j.jaad.2016.11.042

[68] Reich K, Papp KA, Blauvelt A, Tying SK, Sinclair R, Thaci D, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): Results from two randomised controlled, phase 3 trials. *Lancet*. 2017;**390**:276-288. DOI: 10.1016/S0140-6736(17)31279-5

[69] Blauvelt A, Papp KA, Griffiths CEM, Randazzo B, Wasfi Y, Shen YK, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *Journal of the American Academy of Dermatology*. 2017;**76**(3):405-417. DOI: 10.1016/j.jaad.2016.11.041

[70] Langley RG, Tsai TF, Flavin S, Song M, Randazzo B, Wasfi Y, et al. Efficacy and safety of guselkumab in patients with psoriasis who have an inadequate response to ustekinumab: Results of the randomized, double-blind, phase III NAVIGATE trial. *The British Journal of Dermatology*. 2018;**178**:114-123. DOI: 10.1111/bjd.15750

[71] Gordon KB, Duffin KC, Bissonnette R, Prinz JC, Wasfi Y, Li S, et al. A phase 2 trial of guselkumab versus adalimumab for plaque psoriasis.

The New England Journal of Medicine. 2015;**373**(2):136-144. DOI: 10.1056/NEJMoa1501646

[72] Information of the clinical trials. Available from: <https://clinicaltrials.gov/> [Accessed: October 22, 2021]

[73] McGeehan GM, Bukhtiyarov Y, Zhao Y, Shi M, Noto P, Stadanlick J, et al. VTP-43742 is a potent and selective ROR γ t blocker that demonstrates oral efficacy in a mouse model of autoimmunity through suppression of IL-17A production (THER7P.945). *Journal of Immunology* 2015;194 (Supplement 1) 208.5

[74] Gege C. ROR γ t inhibitors as potential back-ups for the phase II candidate VTP-43742 from vitae pharmaceuticals: Patent evaluation of WO2016061160 and US20160122345. *Expert Opinion on Therapeutic Patents*. 2017;**27**:1-8. DOI: 10.1080/13543776.2017.1262350

[75] Takeda. Results for FY2016 Data Book by Takeda Pharmaceutical Company Limited. May 10, 2017. Available from: https://www.takeda.com/siteassets/system/investors/report/quarterlyannouncements/fy2016/fy-2016-q4-announcements-released-on-may-10-2017/qr2016_q4_d1_en.pdf. [Accessed: November 10, 2021]

[76] Jetten AM. Retinoid-related orphan receptors (RORs): Critical roles in development, immunity, circadian rhythm, and cellular metabolism. *Nuclear Receptor Signaling*. 2009;**7**:e003. DOI: 10.11131/2015/101185

[77] Ortiz MA, Piedrafita FJ, Pfahl M, Maki R. TOR: A new orphan receptor expressed in the thymus that can modulate retinoid and thyroid hormone signals. *Molecular Endocrinology*. 1995;**9**(12):1679-1691. DOI: 10.1210/mend.9.12.8614404

[78] Yen HR, Harris TJ, Wada S, Grosso JF, Getnet D, Goldberg MV, et al. Tc17 CD8 T cells: Functional plasticity and subset diversity. *Journal of Immunology*. 2009;**183**(11):7161-7168. DOI: 10.4049/jimmunol.0900368

[79] Sutton CE, Mielke LA, Mills KH. IL-17-producing $\gamma\delta$ T cells and innate lymphoid cells. *European Journal of Immunology*. 2012;**42**:2221-2231. DOI: 10.1002/eji.201242569

[80] Spits H, Cupedo T. Innate lymphoid cells: Emerging insights in development, lineage relationships, and function. *Annual Review of Immunology*. 2012;**30**:647-675. DOI: 10.1146/annurev-immunol-020711-075053

[81] Ruan Q, Kameswaran V, Zhang Y, Zheng S, Sun J, Wang J, et al. The Th17 immune response is controlled by the Rel-ROR γ -ROR γ T transcriptional axis. *The Journal of Experimental Medicine*. 2011;**208**(11):2321-2333. DOI: 10.1084/jem.20110462

[82] Ueda E, Kurebayashi S, Sakaue M, Backlund M, Koller B, Jetten AM. High incidence of T-cell lymphomas in mice deficient in the retinoid-related orphan receptor ROR γ . *Cancer Research*. 2002;**62**(3):901-909

[83] Liljevald M, Rehnberg M, Soderberg M, Ramnegard M, Borjesson J, Luciani D, et al. Retinoid-related orphan receptor γ (ROR γ) adult induced knockout mice develop lymphoblastic lymphoma. *Autoimmunity Reviews*. 2016;**15**(11):1062-1070. DOI: 10.1016/j.autrev.2016.07.036

[84] Kang EG, Wu S, Gupta A, von Mackensen YL, Sienerzki H, Freudenberg JM, et al. A phase I randomized controlled trial to evaluate safety and clinical effect of topically applied GSK2981278 ointment in a

- psoriasis plaque test. *The British Journal of Dermatology*. 2017;**178**:1427-1429. DOI: 10.1111/bjd.16131
- [85] Smith SH, Peredo CE, Takeda Y, Bui T, Neil J, Rickard D, et al. Development of a topical treatment for psoriasis targeting ROR γ : From bench to skin. *PLoS One*. 2016;**11**(2):e0147979. DOI: 10.1371/journal.pone.0147979
- [86] Escalier. Escalies doses first patient with ESR-114 and announces clinical advisory board. 2018. Available from: <https://www.prnewswire.com/news-releases/escalier-doses-first-patient-with-esr-114-and-announces-clinical-advisory-board-300695696.html> [Accessed: October 13, 2021]
- [87] Liu S, Liu D, Shen R, Li D, Hu Q, Yan Y, et al. Discovery of a novel ROR γ antagonist with skin-restricted exposure for topical treatment of mild to moderate psoriasis. *Scientific Reports*. 2021;**11**:9132. DOI: 10.1038/s41598-021-88492-1
- [88] Stark GR, Darnell JE Jr. The JAK-STAT pathway at twenty. *Immunity*. 2012;**36**(4):503-514. DOI: 10.1016/j.immuni.2012.03.013
- [89] Ishizaki M, Muromoto R, Akimoto T, Sekine Y, Kon S, Diwan M, et al. Tyk2 is a therapeutic target for psoriasis-like inflammation. *International Immunology*. 2014;**26**:257-267. DOI: 10.1093/intimm/dxt062
- [90] Sohn SJ, Barrett K, Van Abbema A, Chang C, Kohli PB, Kanda H, et al. A restricted role for TYK2 catalytic activity in human cytokine responses revealed by novel TYK2-selective inhibitors. *Journal of Immunology*. 2013;**191**(5):2205-2216. DOI: 10.4049/jimmunol.1202859
- [91] Papp K, Gordon K, Thaci D, Morota A, Gooderham M, Foley P, et al. Phase 2 trial of selective tyrosine kinase 2 inhibition in psoriasis. *The New England Journal of Medicine*. 2018;**379**(14):1313-1321. DOI: 10.1056/NEJMoa1806382
- [92] Papp KA, Bissonnette R, Gooderham M, Feldman SR, Iversen L, Soung J, et al. Treatment of plaque psoriasis with an ointment formulation of the Janus kinase inhibitor, tofacitinib: A phase 2b randomized clinical trial. *BMC Dermatology*. 2016;**16**(1):15. DOI: 10.1186/s12895-016-0051-4
- [93] FDA approves Opzelura. 2021. Available from: <https://www.drugs.com/newdrugs/fda-approves-opzelura-ruxolitinib-cream-atopic-dermatitis-ad-5666.html> [Accessed: October 22, 2021]
- [94] Punwani N, Scherle P, Flores R, Shi J, Liang J, Yeleswaram S, et al. Preliminary clinical activity of a topical JAK1/2 inhibitor in the treatment of psoriasis. *Journal of the American Academy of Dermatology*. 2012;**67**:658-664. DOI: 10.1016/j.jaad.2011.12.018
- [95] Ortiz-Ibanez K, Alsina MM, Munoz-Santos C. Tofacitinib and other kinase inhibitors in the treatment of psoriasis. *Actas Dermo-Sifiliográficas*. 2013;**104**(4):304-310. DOI: 10.1016/j.adengl.2013.03.002
- [96] Banfield C, Scaramozza M, Zhang W, Kieras E, Page KM, Fensome A, et al. The safety, tolerability, pharmacokinetics, and pharmacodynamics of a TYK2/JAK1 inhibitor (PF-06700841) in healthy subjects and patients with plaque psoriasis. *Journal of Clinical Pharmacology*. 2018;**58**(4):434-447. DOI: 10.1002/jcph.1046
- [97] Durect. DUR-928. 2021. Available from: <https://www.durect.com/pipeline/dur-928/overview/> [Accessed: October 10, 2021]

- [98] Vangipuram R, Alikhan A. Apremilast for the management of moderate to severe plaque psoriasis. *Expert Review of Clinical Pharmacology*. 2017;**10**(4):349-360. DOI: 10.1080/17512433.2017.1293519
- [99] Li H, Zuo J, Tang W. Phosphodiesterase-4 inhibitors for the treatment of inflammatory diseases. *Frontiers in Pharmacology*. 2018;**9**:1048. DOI: 10.3389/fphar.2018.01048
- [100] Pfizer. Pfizer receives FDA approval for EUCRISA™ (crisaborole), a novel non-steroidal topical ointment for mild to moderate atopic dermatitis (Eczema). 2016. Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizer_receives_fda_approval_for_eucrisa_crisaborole_a_novel_non_steroidal_topical_ointment_for_mild_to_moderate_atopic_dermatitis_eczema. [Accessed: October 12, 2021]
- [101] Akama T, Baker SJ, Zhang YK, Hernandez V, Zhou H, Sanders V, et al. Discovery and structure-activity study of a novel benzoxaborole anti-inflammatory agent (AN2728) for the potential topical treatment of psoriasis and atopic dermatitis. *Bioorganic & Medicinal Chemistry Letters*. 2009;**19**:2129-2132. DOI: 10.1016/j.bmcl.2009.03.007
- [102] Moustafa F, Feldman SR. A review of phosphodiesterase-inhibition and the potential role for Phosphodiesterase-4 inhibitors in clinical dermatology. *Dermatology Online Journal*. 2014;**20**(5):1. DOI: 10.5070/D3205022608
- [103] Oba Y, Lone NA. Efficacy and safety of roflumilast in patients with chronic obstructive pulmonary disease: A systematic review and meta-analysis. *Therapeutic Advances in Respiratory Disease*. 2012;**7**(1):13-24. DOI: 10.1177/1753465812466167
- [104] Lebwohl MG, Papp KA, Gold LS, Gooderham MJ, Kircik LH, Draelos ZD. Trial of Roflumilast cream for chronic plaque psoriasis. *The New England Journal of Medicine*. 2020;**383**:229-239. DOI: 10.1056/NEJMoa2000073
- [105] Milakovic M, Gooderham MJ. Phosphodiesterase-4 inhibition in psoriasis. *Psoriasis*. 2021;**11**:21-29. DOI: 10.2147/PTT.S303634
- [106] Richardson WH, Schmidt TM, Neelson KH. Identification of an anthraquinone pigment and a hydroxystilbene antibiotic from *Xenorhabdus luminescens*. *Applied and Environmental Microbiology*. 1988;**54**(6):1602-1605. DOI: 10.1128/aem.54.6.1602-1605.1988
- [107] Smith SH, Jayawickreme C, Rickard DJ, Nicodeme E, Bui T, Simmons C, et al. Tapinarof is a natural AhR agonist that resolves skin inflammation in mice and humans. *The Journal of Investigative Dermatology*. 2017;**137**(10):2110-2119. DOI: 10.1016/j.jid.2017.05.004
- [108] Veldhoen M, Hirota K, Westendorf AM, Buer J, Dumoutier L, Renaud JC, et al. The aryl hydrocarbon receptor links TH17-cell-mediated autoimmunity to environmental toxins. *Nature*. 2008;**453**:106-109. DOI: 10.1038/nature06881
- [109] Bissonnette R, Bolduc C, Maari C, Nigen S, Webster JM, Tang L, et al. Efficacy and safety of topical WBI-1001 in patients with mild to moderate psoriasis: Results from a randomized double-blind placebo-controlled, phase II trials. *Journal of the European Academy of Dermatology and Venereology*. 2012;**26**:1516-1521. DOI: 10.1111/j.1468-3083.2011.04332.x
- [110] GSK. GSK sells psoriasis/Dermatitis candidate tapinarof to Dermavant.

2018. Available from: <https://www.genengnews.com/topics/drug-discovery/gsk-sells-psoriasis-dermatitis-candidate-tapinarof-to-dermavant/> [Accessed: October 12, 2021]

[111] Dermavant. Dermavant showcases new long-term data from Phase 3 +- PSOARING 3 trial of tapinarof in patients with plaque psoriasis at the 30th EADV Virtual Congress. 2021. Available from: <https://www.dermavant.com/dermavant-showcases-new-long-term-data-from-phase-3-psoaring-3-trial-at-the-30th-eadv-virtual-congress/> [Accessed: October 12, 2021]