INTERLEUKIN-17 AND INTERLEUKIN-23: A NARRATIVE REVIEW OF MECHANISMS OF ACTION IN PSORIASIS AND ASSOCIATED COMORBIDITIES

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ABSTRACT

Psoriasis is an immune-mediated inflammatory skin disease associated with numerous inflammatory comorbidities, including increased cardiovascular risk. The interleukin (IL)-23/IL-17 axis plays a central role in the immunopathogenesis of psoriasis and related comorbidities by acting to stimulate keratinocyte hyperproliferation and feed-forwarding circuits of perpetual T cell-mediated inflammation. IL-17 plays an important role in the downstream portion of the psoriatic inflammatory cascade. This review discusses the distinct mechanisms of action of IL-17 and IL-23 in the immunopathogenesis of psoriasis and related comorbidities plus the significant therapeutic benefits of selectively inhibiting these cytokines in patients with moderate to severe plaque psoriasis.

Keywords: Comorbidities; Cytokines; Inflammation; Interleukin-17; Interleukin-23; Psoriasis
Key Summary Points

Interleukin (IL)-17 and IL-23 are involved in the immunopathogenesis of psoriasis (PsO) and related comorbidities by acting to stimulate keratinocyte hyperproliferation and feed-forwarding circuits of perpetual T cell-mediated inflammation.

IL-17 and IL-23 have unique mechanisms of action in the immunopathogenesis of PsO.

Additionally, elevated levels of IL-17 and IL-23 in patients with moderate to severe PsO promote chronic subclinical inflammation that increases the risk of comorbidities.

Both IL-17 and IL-23 are implicated in PsA pathogenesis; however, IL-17-mediated inflammation may be more central in the development of cardiometabolic comorbidities and axial spondyloarthritis, whereas IL-23 may be more important in IBD immunopathogenesis.

Given the specificity of the IL-23/IL-17A axis in modulating the differentiation and activation of specialized cells involved in skin and joint inflammation, selective blockade of IL-23 and IL-17A is more efficacious than traditional biologic therapies in targeting the psoriatic disease process.

INTRODUCTION

Chronic plaque psoriasis (PsO) is an immune-mediated inflammatory disease characterized by cutaneous, erythematous, indurated, scaly plaques [1, 2]. PsO has been reported to affect 3.2% of adults (≥ 20 years of age) in the USA [3]. It is associated with multiple comorbidities, including increased cardiovascular (CV) risk and psoriatic arthritis (PsA), plus many other systemic conditions [4]. The cardiometabolic issues have been shown to reduce the life expectancy of patients with severe PsO by approximately 3–4 years [5].

PsO immunopathogenesis is driven by circulating pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-17, IL-23 and both type 1 and type 2 interferons (IFNs) including IFNα/β and IFNγ. These cytokines are produced by T-helper (Th) cells and activated dendritic cells (DCs) that infiltrate the skin and remain as memory T cells in lesional skin [6, 7]; this observation strongly supports the well-known observation that PsO lesions frequently recur in the same anatomical area [8]. Upregulation of these molecular pathways stimulates keratinocyte hyperproliferation and T cell-mediated inflammation [9, 10]. This important inflammatory burden plays a significant role in adding to the increased risk of multiple inflammatory comorbidities [11].

The IL-23/IL-17 immune axis plays a central role in PsO onset, perpetuation of disease and development of PsA [12] and other inflammatory comorbidities [13, 14]. This review discusses the mechanisms of action of IL-17 and IL-23 in PsO immunopathogenesis and related comorbidities and the benefits of biologic therapies that inhibit these cytokines.

STATEMENT OF LITERATURE SEARCH

For this narrative review, articles were identified by a series of PubMed searches between August 2018 and August 2020. Search terms included “IL-17,” “IL-23,” “(IL-17 OR IL-23) AND (psoriasis OR psoriatic arthritis OR PsA OR ankylosing spondylitis OR axial spondyloarthritis OR...
axSpA OR psoriasis comorbidities),” “psoriasis pathogenesis” and “psoriasis AND cytokines.” Publications detailing the roles of IL-17 and/or IL-23 in the pathogenesis and pathophysiology of PsO, PsA, ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (nr-axSpA) or associated comorbidities were included. Irrelevant references were excluded from consideration. References cited within the included articles, as well as those previously known to the authors, were considered based on these criteria. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

ORIGINS OF THE IL-17 AND THE IL-23 PATHWAYS

The IL-17 and IL-23 pathways are central to PsO (Fig. 1) [15, 16]. TNF-α is a target of four approved PsO therapies and plays an indirect role in disease pathogenesis by promoting adaptive immune effects of the IL-23/IL-17 axis [17]. The role of IL-23 in PsO onset and continuation is considered to be due to its effects on IL-17—a key effector cytokine of the feed-forward inflammatory cycles that perpetuate inflammation [15]. Such signaling loops are the hallmarks of innate immune responses in inflammatory and infectious diseases associated with rash, fever, arthritis, skin inflammation, osteopathies and central nervous system damage [18].

IL-17 has more direct effects on DC distribution and activation than TNF-α; however, synergism between IL-17A and TNF-α modulates keratinocyte gene responses in psoriatic lesions [19, 20]. This interaction is further amplified by IL-17C—the most highly expressed IL-17 in psoriatic lesions [21].

Role of IL-17

In mammals, IL-17 comprises six homologs that are considered to function as homodimers [22]. IL-17 is produced by Th17 cells in response to stimulation by IL-23 and other cytokines [13]. In addition to Th17 cells, innate lymphoid cells (ILCs), mast cells, neutrophils and γδ T cells may be independent sources of IL-17A production in patients with PsO [23]. IL-17A is released from neutrophils and mast cells during specialized immune-mediated cell death in which proteins bind to chromatin threads to form extracellular traps [24, 25]. However, data are conflicting on whether neutrophils are a major source of IL-17A in PsO; some studies demonstrate IL-17A expression in highly purified human neutrophils, while other studies have failed to detect IL-17A [25–27].

In response to increased IL-17A expression, cells with high concentrations of IL-17 receptors release pro-inflammatory chemokines, cytokines and antimicrobial peptides [28, 29]. The effects of immune cytokines as transcriptional activators of keratinocyte gene products, and auto-antigen stimulation of T-cell responses create feed-forward inflammatory circuits that perpetuate the T-cell activation and inflammation associated with PsO [15]. Stimulation of keratinocytes by IL-17A triggers production of C–C motif chemokine ligand 20, and other chemo-attractants recruit CCR6+ T cells, including IL-17-producing T cells (T17), mature myeloid DCs and other inflammatory cells. This creates a cycle of ongoing inflammatory responses [15, 30]. IL-17A also stimulates keratinocytes to produce IL-19, leading to further keratinocyte proliferation [15]. Cellular levels of the auto-antigens cathelicidin (LL37) and a disintegrin-like and metalloprotease domain containing thrombospondin type 1 motif-like 5 (ADAMTSL5) [31] support this feed-forward hypothesis, as IL-17A blockade decreases levels of LL37- and ADAMTSL5-producing cells in psoriatic lesions [32].

In patients with PsO in remission, tissue-resident memory T cells in epidermal skin compartments have the ability to maintain and potentially drive disease recurrence [33]. Years after withdrawal of successful PsO treatment, CD8+ tissue-resident memory T cells maintain elevated levels of IL-17A, possibly driving inflammation and recruitment of circulating leukocytes into tissue with triggers of disease [33]. It has recently been demonstrated that oligoclonal populations of IL-17–producing T
cells remain enriched in clinically resolved psoriatic lesions; of pathogenic T cells identified in active and clinically resolved psoriatic lesions, ≥ 99% were found to be αβ T cells [34].

**Role of IL-23**

IL-23 is a heterodimeric cytokine that shares a common p40 subunit with IL-12 and a p19 subunit common to IL-23 and IL-39 [35, 36]. The p40 and p19 subunits of IL-23 are overexpressed in PsO plaques, and variations in genes encoding p19 and its receptor are associated with an increased risk of PsO [35, 36]. IL-23 is produced by many types of cells, including dermal myeloid DCs, macrophages and epidermal Langerhans cells [15]. It is regulated by Toll-like receptor signaling and is enhanced by TNF-α, IFN-γ and transcription factors [37, 38]. The IL-23 receptor (IL-23R) is expressed on memory T cells, natural killer cells, neutrophils, mast cells, ILCs and macrophages [38]. IL-23 binding to its cognate receptor forms an IL-23/IL-23R complex that stimulates ILC differentiation and triggers CD4+, CD8+ and γδ T cells to synthesize IL-17 and other pro-inflammatory cytokines [39]. IL-23 also induces macrophages to produce TNF-α, stimulates keratinocyte proliferation in the absence of IL-17A and promotes further IL-23R expression, thus creating a self-amplifying loop [15, 39, 40].

**Differences Between the IL-17 and IL-23 Pathways**

IL-17A overproduction triggers the perpetual cycle of inflammation that characterizes PsO pathogenesis—which includes a cascade of cytokine, chemokine and antimicrobial peptide actions that induce epidermal hyperplasia—and innate immune responses [7, 15, 16]. IL-23 is a key upstream regulator of IL-17A production by stimulating differentiation, activation, proliferation and survival of Th17 cells. Because IL-23 does not regulate all cellular mechanisms of IL-17A production, targeting IL-23 does not seem to increase the risk of candidiasis that has been observed in the small percentage of patients (< 5%) treated with IL-17A inhibitors [16, 41]. However, agents that directly target the IL-17 pathway act more downstream in the psoriatic inflammatory cascade [15], providing a disease-specific treatment with a rapid onset of action [42–45].

**PSORIASIS COMORBIDITIES AND THE ROLE OF IL-17 AND IL-23**

Elevated levels of systemic pro-inflammatory cytokine in patients with moderate to severe PsO promote chronic subclinical inflammation that increases the risk of comorbidities, including PsA, CV disease, diabetes, obesity, dyslipidemia, hypertension, inflammatory bowel disease (IBD), nonalcoholic fatty liver disease and depression [4, 46, 47]. IL-17 and IL-23 are implicated in PsA pathogenesis; however, IL-17-mediated inflammation may be more central in the development of cardiometabolic comorbidities [48, 49] and IL-23 in IBD immunopathogenesis [50].

To treat moderate to severe plaque PsO, six biologic therapies targeting IL-17A or IL-23 are currently approved: secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab and risankizumab. Secukinumab is a fully human IgG1κ monoclonal antibody (mAb) [51], and ixekizumab is a humanized IgG4 mAb [52, 53]; these agents selectively bind and neutralize IL-17A. Brodalumab is a fully human IgG2 mAb that binds to the IL-17A receptor in a nonactivating manner and thus inhibits IL-17A, IL-17C, IL-17E and IL-17F [54]. Seminal mechanistic studies of inflammatory immune responses elicited by IL-17 and disrupted by anti–IL-17 mAbs have confirmed that IL-17A inhibition blocks pathogenic mechanisms of psoriatic inflammation [19, 55, 56].

Anti–IL-23 agents include guselkumab, a human IgG1κ mAb; tildrakizumab, a humanized IgG1κ mAb; and risankizumab, a humanized IgG1 mAb. Both guselkumab and tildrakizumab bind the p19 subunit of IL-23, preventing formation of a receptor complex [36, 57]. Risankizumab binds and neutralizes the p19 subunit of IL-23 [58]. Mutations in p19 and its receptor IL-23R are associated with a risk of PsO [59].
The six approved IL-17A and IL-23 inhibitors appear more efficacious than biologic therapies that are less specific such as the four TNF-α inhibitors, adalimumab, etanercept, certolizumab pegol and infliximab, and the single IL-12/23 inhibitor ustekinumab [52, 60–62]. Significant improvements in skin manifestations of psoriatic disease are achieved in approximately 90% of patients with approved IL-17A or IL-23 inhibitors [63].

Additional IL-17 and IL-23 therapies are in late-stage clinical development. Bimekizumab is a humanized IgG1 mAb that selectively neutralizes IL-17A and IL-17F and is being studied in PsO [64], PsA [65] and axial spondyloarthritis. Mirikizumab is a p19 antagonist of IL-23 under investigation for the treatment of PsO [66], ulcerative colitis [67] and Crohn’s disease (CD) [39, 68].

Psoriatic Arthritis

Approximately 30% of patients with PsO develop PsA within 10 years of the onset of their skin disease [69, 70]. Delay of PsA diagnosis for as little as 6 months can result in permanent joint erosions [71]. These erosions may be evident in 40–60% of patients within the first year of diagnosis [72], and 55% of patients have been found to have ≥5 deformed joints over 10 years of disease [70]. Pathogenic features of PsA include elevated synovial fluid levels of IL-17 and increased expression of IL-17A receptor by synoviocytes [12, 73]. Increased levels of IL-17A and IL-23 in PsA lead to upregulation of other cytokines (e.g. IL-6 and IL-8), matrix metalloproteinases and the receptor activator of NF-κB (RANK), which are associated with pathogenic changes, bone resorption, bone matrix structure changes and osteoclastogenesis [73–76].

Animal PsA models demonstrate that IL-23 and IL-17 induce skin and joint inflammation, but distinct cellular pathways regulate these outcomes [77]. Axial involvement in PsA is predominantly driven by IL-17 with the induction of RANK ligand and RANK in stromal cells and osteoclast precursors, respectively, leading to pathologic osteoclast differentiation [78–80]. In contrast, IL-23 induces co-stimulatory pathways via immunoreceptors expressed in myeloid osteoclast precursors [81]. The presence and severity of dactylitis and enthesis is strongly correlated with HLA-B27 misfolding, which triggers upregulation of IL-23 and induction of the IL-17 axis [82]. Experimental models show that upregulation of pro-inflammatory cytokines of the IL-23/IL-17 pathway induce joint swelling, skin changes and nail deformities characteristic of PsA [77]. In a murine model, treatment with IL-17A and IL-17F inhibitors decreased levels of inflammatory cytokines and showed efficacy in treatment of skin inflammation mimicking PsO [83].

IL-17A is central in the pathogenesis of joint destruction and bone erosion in PsA, with elevated levels of IL-17A and/or its receptor in synovial tissue, osteoblasts, osteoclasts and chondrocytes [80, 84]. Studies of secukinumab and ixekizumab support the mechanistic role of IL-17A in PsA immunopathogenesis, as inhibition of this cytokine improves joint symptoms and prevents joint destruction [85]. Patients receiving secukinumab or ixekizumab also report significant improvements in physical functioning and quality of life and achieve complete or near complete skin clearance [53, 86–89]. Secukinumab and ixekizumab are both approved for the treatment of active PsA, and both prevent joint destruction [90, 91].

The efficacy of targeted IL-23 inhibition in PsA has been confirmed in large-scale studies. Results from the phase 3 DISCOVER-1 and DISCOVER-2 trials show efficacy of guselkumab in patients with active PsA despite treatment with standard nonbiologic therapies, leading to its recent approval for the treatment of active PsA [92, 93]. Phase 3 studies of tildrakizumab (NCT03552276) and risankizumab (NCT03671148 and NCT03675308) are also ongoing for PsA. The IL-12/23 inhibitor ustekinumab is approved for the treatment of active PsA, despite its non–placebo-adjusted ACR20 scores being 18–35% lower than those for TNF-α and IL-17A agents approved for PsA (secukinumab and ixekizumab) [62]. In March 2019, risankizumab received its first global approval in Japan for the treatment of adults with PsO and PsA [94], based on positive results from the
SustaiMM phase 2/3 trial [95]. Injection-site reactions (ISRs) have been recorded in clinical trials of many biologic agents for PsO and PsA, with the majority being of mild to moderate intensity. With adalimumab, etanercept, ixekizumab and guselkumab, ISRs are among the most common adverse events [96–99]. With secukinumab, ISRs affect < 1% of patients [100], whereas ixekizumab has more frequent and longer-lasting ISRs [98]. Most ISRs for all biologic agents mentioned resolve without any medical intervention; however, persistent ISRs can be treated with oral antihistamines or prevented by switching to another biologic therapy [101].

Cardiovascular and Metabolic Diseases

Mild and severe PsOs are both associated with an increased risk of myocardial infarction and stroke, while severe PsO is associated with a significantly increased risk of CV mortality [102]. In three cross-sectional studies, moderate to severe coronary calcification was five times higher in patients with PsO than in healthy controls and similar to that in patients with type 2 diabetes [103]. CV risk in patients with severe PsO is independent of traditional risk factors and is associated with significant mortality [104]. The relative risk of CV mortality is 2.69 for a 40-year-old patient with severe PsO versus a matched healthy control [104]. CV disease in patients with PsO is also associated with an increased prevalence of metabolic disorders; patients with PsO are more than twice as likely as the general population to have metabolic syndrome [14, 105].

Similarities exist between the pathophysiology of PsO, atherosclerosis and metabolic syndrome [106]. This includes the immunology and pathology of the activation of myeloid DCs and endothelial cells, promoting differentiation of Th1 and Th17 cells and secretion of pro-inflammatory cytokines such as TNF-α, IFN-γ, IL-17A and IL-22 [49, 105]. In PsO and atherosclerosis, IL-17 and TNF-α synergistically activate NF-kB signaling and mitogen-activated protein kinases to induce neutrophil-attracting chemokines and other inflammation modulators [107, 108]. Using the KC-Tie2 doxycycline-repressible (Dox-off) murine model of psoriasiform skin disease, prolonged elevations in IL-17, TNF-α and C–C motif chemokine ligand-2 have been found to increase aortic inflammation and thrombosis [109]. This thrombosis phenotype can be attenuated upon elimination of skin inflammation with doxycycline[109] or through inhibition of IL-17A or IL-23 [110]; this effect is potentially mediated by reduction of skin IL-6 [111]. These results suggest that chronic systemic inflammation associated with PsO is likely the main cause of the increased risk of adverse CV outcomes [109].

IL-17 also contributes to the pathophysiology of hyperlipidemia, hypertension, renal disease and obesity. Increased IL-17 production exacerbates hyperlipidemia by triggering immune responses against oxidized low-density lipoprotein and collagen V [112, 113]. In hypertension and renal disease models, IL-17 promotes inflammation by stimulating neutrophil chemo-attractants and increasing renal artery stiffening, possibly through upregulation of type I collagen deposition [114–117]. In obesity, a common issue in patients with moderate to severe PsO, circulating IL-17A promotes production of vascular endothelial growth factor and acts synergistically with adipokines to perpetuate inflammation, angiogenesis and endothelial dysfunction [118].

The phase 4 ObetPso-S study (NCT03055494) explored the effects of secukinumab versus placebo on the expression of inflammatory genes in patients with moderate to severe chronic plaque PsO. Preliminary results indicate that treatment responses observed with secukinumab correspond to normalized inflammatory marker and immune cell levels [119]. Another phase 4, open-label study (METABOLIX, NCT03440736) is investigating whether treatment with secukinumab and lifestyle changes can improve metabolic status in patients with PsO with metabolic syndrome; results are expected in 2021.

A series of studies on vascular inflammation in PsO (VIP) is evaluating the effects of biologic therapies on vascular inflammation and CV biomarkers. In the adalimumab study (VIP-A), TNF-α inhibition reduced levels of the

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inflammatory markers C-reactive protein and IL-6 versus placebo or phototherapy, but not vascular inflammation [120]. In the ustekinumab study (VIP-U), 12 weeks of treatment reduced aortic vascular inflammation by 6.6% versus a 12.1% increase with placebo ($P = 0.001$) [121]. However, no differences in aortic vascular inflammation were observed after 52 weeks of ustekinumab treatment [122]. In the secukinumab study (VIP-S), although TNF-α and ferritin levels were reduced and fetuin-A levels increased after 52 weeks of secukinumab treatment (all $P < 0.05$ versus placebo), no significant changes in aortic vascular inflammation versus placebo were observed [123].

Axial Spondyloarthritis

The IL-23/IL-17 axis has been implicated in the pathogenesis of axial spondyloarthritis (axSpA), including AS and nr-axSpA [124, 125]. PsO is observed in 10% of patients with AS [126]. In patients with AS, genes in the Th17 pathway are overexpressed and serum levels of IL-17 and IL-23 are elevated [127]. IL-17A inhibition with secukinumab or ixekizumab significantly reduces signs and symptoms of AS [128–130] and nr-axSpA [131, 132]. In contrast, data on the effects of IL-23 inhibition in axSpA are limited. In a phase 2 study, treatment with risankizumab did not improve signs and symptoms of AS versus placebo [133]. The significant efficacy of IL-17A inhibitors in axSpA and the lack of efficacy with the IL-23 inhibitor risankizumab [133] suggest that IL-17A modulates a pathogenic pathway in axSpA, which is independent of IL-23 signaling.

Inflammatory Bowel Disease

IBD is approximately four times more prevalent in patients with PsO than in the general population [134], suggesting a genetic overlap of the two diseases [135]. IL-23 has been linked to murine chronic intestinal inflammation, and genome-wide association studies have implicated IL-23 gene variants in IBD [136]. However, contrasting data suggest a role for IL-17A in gastrointestinal homeostasis and tissue repair rather than in driving inflammation as in PsO pathogenesis [137]. In clinical studies, patients with IBD have achieved significantly higher rates of clinical and endoscopic remission with IL-12/23 or IL-23 inhibitors than with placebo [50]. Ustekinumab is approved for the treatment of moderate to severe active CD and is in late-stage development for ulcerative colitis; IBD trials are also ongoing for several IL-23 inhibitors [138], with positive results reported for risankizumab in CD [139]. Conversely, IL-17A inhibitors have failed to demonstrate efficacy in CD, despite their clear efficacy in PsO [140, 141]. The local environment of Th17 cells in the gut and skin may differ, or IL-23 may act via an IL-17-independent pathway to promote intestinal inflammation in patients with IBD [50]. Although small clusters of new IBD cases have been reported among patients with PsO, PsA or AS using IL-17A inhibitors, IBD events were rare (< 1%), and their incidence did not increase over time [135, 137, 142]. The effects of IL-17A inhibition on IBD may be two-fold and conflicting, either decreasing inflammation or possibly worsening the residual function of an already impaired epithelial barrier [137].

EXPERT COMMENTARY

Data from preclinical and clinical studies provide strong evidence that IL-17A and IL-23 are key mechanistic drivers of PsO immunopathogenesis. Targeting IL-17A and IL-23 cytokines provides skin clearance superior to that of currently approved TNF-α inhibitors or ustekinumab [51, 52, 58, 61, 143].

In patients with moderate to severe chronic plaque PsO, treatment with approved IL-17A or IL-23 inhibitors is well tolerated. Complete or near complete skin clearance is seen in the majority of patients [53, 86–88]. Across pivotal PsO phase 3 studies, > 50% of treated patients achieved ≥ 90% improvement in Psoriasis Area and Severity Index scores [63]. Additionally, secukinumab, ixekizumab and guselkumab are effective in more difficult-to-treat disease subtypes, including palmoplantar, scalp, nail and genital PsO [144–149]. Available data for IL-17 inhibitors suggest that primary and secondary nonresponse can be treated by switching to
IL-17A and IL-23 inhibitors are better tolerated than methotrexate and TNF-α inhibitors and show a safety profile comparable to that of ustekinumab [152]. Use of IL-17A inhibitors is associated with an increased risk of mucocutaneous candidiasis (< 5% of treated patients), but it does not lead to treatment discontinuation [16]. Reports of neutropenia (0.7 events per 100 patient-years of exposure) and IBD (< 1%) are rare with approved IL-17A inhibitors [128, 137]. In phase 3 studies of brodalumab, three patients attempted suicide with one completion [153]. No major safety signals have been identified with guselkumab, tildrakizumab or risankizumab. IL-23 inhibitors do not appear to be associated with an increased risk of candidiasis or IBD; however, safety data from real-world registries are needed to confirm the full tolerability of targeted IL-23 inhibition [41, 152].

**CONCLUSIONS**

IL-17 and IL-23 have unique mechanisms of action in PsO immunopathogenesis, with IL-17 being an important cytokine in the PsO inflammatory cascade. New biologic agents blocking IL-17A and/or IL-23 are more efficacious than traditional biologic therapies that are less specific in targeting the psoriatic disease process. Given the specificity of the IL-23/IL-17A axis in modulating the differentiation and activation of specialized cells involved in skin and joint inflammation, selective blockade of IL-23 and IL-17A is more efficacious than traditional biologic therapies. The contribution of each pathologic mechanism to the clinical manifestations of PsO, PsA and other inflammatory comorbidities is currently under evaluation in multiple clinical trials.
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