Targeting IL-17 in psoriatic arthritis
Elizabeth A. Wang1, Erika Suzuki2, Emanuel Maverakis1, Iannis E. Adamopoulos2-3

Abstract
Psoriatic arthritis (PsA) is a chronic and progressive inflammatory arthritis intimately associated with psoriasis, and can be an impairing disease that leads to reduced quality of life and significant morbidity. Treatment often requires TNF antagonists, yet many patients with PsA are not responsive to the standard anti-TNF therapies. The interleukin-17 (IL-17)/IL-17 receptor (IL-17R) family has recently been implicated in the pathogenesis of PsA and psoriasis. Much enthusiasm has been generated for the development of biologics that target the IL-17 signaling pathway directly or indirectly, many of which have produced striking results in the setting of psoriasis and PsA. Herein, we review the role of IL-17 and the IL-17 receptor (IL-17R) in the pathogenesis of PsA, as well as the clinical evidence for IL-17 and IL-17R targeted therapeutics.

Keywords: Psoriatic arthritis, psoriasis, interleukin-17

Introduction
Psoriatic arthritis (PsA) is a chronic, inflammatory, and heterogeneous disease that can affect various distinct anatomical sites including peripheral and axial joints, entheses, skin and nails (1). PsA is grouped together with the other spondylarthropathies—i.e., arthritic diseases affecting the peripheral or axial spine. PsA is a seronegative arthritis not commonly associated with specific autoantigens or autoantibodies (2, 3). Although PsA is a form of inflammatory arthritis that shares characteristics with other arthritic diseases including rheumatoid arthritis (RA), it is a distinct entity defined in part by concomitant or preceding psoriatic skin findings.

Clinical features of PsA
In the vast majority of patients with PsA, psoriatic features commonly precede the development of bone or joint involvement; however, joint pain or bone destruction can also precede the emergence of psoriatic lesions. The transition from having skin-only manifestations of psoriasis (PsO) to concomitant PsA occurs in up to 40% of psoriasis patients (4, 5). Histologically, psoriasis is characterized by epidermal hyperplasia, hyperkeratosis, parakeratosis, Munro's microabscesses (neutrophilic granulocytes at the epidermis) and mixed dermal infiltrates including T cells, dendritic cells and macrophages, which together lead to the clinical features of raised erythematous skin with overlying silvery plaques (6, 7).

With respect to PsA, the most common clinical manifestation is a symmetrical polyarthritis that affects the joints equally. It resembles a rheumatoid-like pattern; however, it is differentiated from RA by the presence of distal interphalangeal joint involvement and the absence of subcutaneous nodules. Patients who are left untreated may experience progressive joint damage and deformity secondary to sustained inflammation, resulting in morbidity and disability. Dactylitis is also an important feature of PsA, and is a combination of enthesitis of the tendons or ligaments, and synovitis affecting joints in the digit (8). Enthesitis may occur at any site in PsA (8). Histologic changes in the joint are similar to those observed in common forms of arthritis such as RA; however, in PsA there is presence of enthesitis and increased synovial vascularity (9, 10). Increased monocytes, mast cells, neutrophils and mature monocytes CD163+ cells are also observed in PsA (11, 12).

Epidemiology
The precise etiology of PsA is not well understood, though it is recognized as a multifactorial disease whose pathogenesis arises from various genetic, environmental and immunological factors. The prevalence of PsA varies widely among different countries, from 1 per 100,000 in Japan, to 250 per 100,000 in the United States and to 470 per 100,000 in Australia (13-15). However, these geoepidemiological differences may be further complicated by environmental and immunological factors and genetic susceptibility. In addition to physical trauma, as evidenced by the Koebner phenomenon in which penetrating cuts in psoriatic skin lead to further psoriatic plaque formation, other environmental factors such as infectious agents, recurrent oral ulcers, or HIV infection play a role (16, 17).
Interleukin 17 (IL-17) is a common denominator of various inflammatory diseases and has a crucial role in the pathogenesis of PsA and psoriasis. Experimental evidence, from psoriatic lesions and synovial fluid in humans to psoriatic-like and arthritis mouse models, support the development of therapies targeting the IL-17 pathway. Herein, we review the role of the IL-17 pathway in the pathogenesis of PsA, as well as the clinical evidence for IL-17 and IL-17 receptor (IL-17R) targeted therapeutics.

IL-17 (or IL-17A) is a homodimeric disulfide-linked glycoprotein and the most widely studied of the IL-17 family of cytokines (IL-17, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F) (18). Th17 cells, gd T cells, and various other immune cells have been demonstrated to secrete IL-17 (19, 20). IL-17 and IL-17F share the greatest homology, and can form heterodimers, which also bind IL-17R. IL-17R is commonly expressed on epithelial cells, vascular endothelial cells, keratinocytes and fibroblasts as well as on cells of hematopoietic lineage, including monocytes, neutrophils, T and B cells, γδ T cells, LTI cells and other innate-like lymphocytes (21, 22).

The dimeric IL-17R complex consists of IL-17RA and IL-17RC subunits (22, 23). IL-17 has differential affinities for binding to IL-17RA and IL-17RC, though the precise binding kinetics are not well defined under specific inflammatory conditions. Interestingly, the distribution of IL-17R is also not uniform. Although IL-17RA is ubiquitously expressed in cells of hematopoietic cell origin, IL-17RC demonstrates variable expression. The variable expression observed with IL-17RC suggests that it may be rapidly internalized upon binding, differentially expressed under homeostatic conditions or bind additional, possibly unidentified ligands. Additionally, alternatively spliced soluble forms of IL-17RA and IL-17RC have recently been identified and are thought to negatively regulate IL-17 signaling (21, 22).

Binding of IL-17 to IL-17R leads to the recruitment of an adaptor molecule, Act1, which associates with inducible IkB kinase (IKK) and tumor necrosis factor receptor-associated factor (TRAF) proteins. Single nucleotide polymorphisms in TRAF3IP2 (Act1) have linked IL-17-mediated immune regulation to PsA disease pathology (24). Interestingly, the Act1 mutation that has been associated with PsA susceptibility is suggested to differentially regulate TRAF2/5 and TRAF6 binding and downstream signaling. Phosphorylation of IKK and binding of TRAF2 and TRAF5 lead to CXCL1 chemokine stabilization to drive neutrophil recruitment, whereas binding of TRAF6 leads to activation of mitogen-activated protein kinase (MAPK) and transforming growth factor b activated kinase-1 (TAK1), to induce translocation and transcriptional activity of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activator protein (AP-1), CCAAT-enhancer-binding protein (C/EBP) and NF-κB (25-27). The activation of these transcription factors leads to the secretion of various trophic factors including CXCL1, CXCL2, CXCL8, CCL2, CCL7, granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) to promote myeloid cells and granulocyte recruitment, development and inflammatory effector function. Moreover, recent studies have highlighted the diverse heterogeneity of myeloid cells and granulocytes suggesting that IL-17 may mediate yet to be defined non-redundant inflammatory pathways, which are distinct from its classical activation within a particular disease.

### IL-17 in PsA

IL-17 plays multiple critical roles in the pathogenesis of PsA and psoriasis (28). It is known to act on keratinocytes and synovial cells to produce pro-inflammatory mediators, bridging the innate and adaptive immune systems to sustain chronic inflammation (Figure 1) (28). IL-17 has protective roles in host defense at epithelial borders and defense against fungal and bacterial pathogens, as well as inflammatory roles in autoimmunity. Although IL-17 is a common denominator of many inflammatory diseases, the mechanisms that govern IL-17-mediated disease may differ. Moreover, IL-17 is commonly evaluated in relation to IL-23...
Table 1. IL-17 and IL-17R targeted therapeutics for PsA in development

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Sponsor</th>
<th>Target</th>
<th>Type</th>
<th>Clinical/Development Status for PsA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secukinumab</td>
<td>Novartis</td>
<td>IL-17</td>
<td>Fully human mAb</td>
<td>Marketed</td>
</tr>
<tr>
<td>Ixekizumab</td>
<td>Eli Lilly</td>
<td>IL-17</td>
<td>Humanized IgG4 mAb</td>
<td>Registered (Lilly announced regulatory submission to FDA for psoriatic arthritis in 2017)</td>
</tr>
<tr>
<td>Brodalumab</td>
<td>Valient</td>
<td>IL-17RA</td>
<td>Fully human IgG2 mAb</td>
<td>Phase III (56)</td>
</tr>
<tr>
<td>RG7624</td>
<td>Genentech</td>
<td>IL-17/F</td>
<td>Humanized IgG1 mAb</td>
<td>Phase Ia</td>
</tr>
<tr>
<td>ABT-122</td>
<td>AbbVie</td>
<td>IL-17/TNF</td>
<td>Humanized mAb</td>
<td>Phase II (57)</td>
</tr>
<tr>
<td>COVA322</td>
<td>Covagen</td>
<td>IL-17/TNF</td>
<td>FynomAb</td>
<td>Preclinical (58)</td>
</tr>
<tr>
<td>SCH 900117</td>
<td>Merck</td>
<td>IL-17</td>
<td>Humanized mAb</td>
<td>Phase I for RA, not yet in PsA</td>
</tr>
</tbody>
</table>

*Based on ongoing clinical trials according to clinicaltrials.gov, as of January 2017

*Based on Pharmaceutical Research and Manufacturers of America, Biologic Medicines in Development

and T cells, yet alternative pathways may exist in promoting pathogenicity at different stages of the disease. IL-17 is mechanistically relevant to PsA as IL-17 and other cytokines such as TNF are activators of NFκB, a key intracellular regulator of the innate immune that triggers transcription of several genes involved in the pathogenesis of PsA (29, 30). For instance, the receptor activator of nuclear factor kB ligand (RANKL) triggers the differentiation of osteoclast precursor cells into activated osteoclasts, resulting in bone resorption and subsequently joint deformity in PsA (31).

Experimental evidence in humans and mouse models has supported the development of IL-17-targeted therapies. At the clinical level, IL-17 and IL-17-producing cells have been found in the serum, psoriatic lesions, and within the synovial fluid of PsA patients-findings that have been shown to correlate with disease activity (32-34). It is likely that the IL-23/IL-17A axis is in fact essential to maintaining entheseal and joint inflammation in patients with PsA (35, 36). In addition, synovial fibroblasts isolated from PsA patients also contain elevated IL-17R expression and secrete increased IL-6, CXCL8 and MMP3 ex vivo compared to osteoarthritis patients (37).

We and others have shown using various animal models the importance of myeloid cells in IL-17-induced pathological features that resemble the human PsA (38, 39). Indeed IL-17 gene transfer is sufficient to induce the expansion of osteoclast precursors and concomitant elevation of biomarkers indicative of bone resorption (40) in parallel with epidermal hyperplasia hallmark phenotypic features of PsA. This occurred at a time preceding noticeable joint inflammation, and suggested that IL-17A is critical for the induction of pathological bone resorption seen in PsA through direct activation of osteoclast precursors. Other groups have also shown evidence for crosstalk between IL-17A-mediated skin inflammation and bone loss. In fact, in mice with IL-17A-induced chronic skin inflammation, IL-17A inhibited osteoblast and osteocyte function through inhibition of Wnt signaling. Blocking IL-17A restored bone formation in vivo (41). Similarly, in a model of inflammatory arthritis, IL-17A deficiency promoted periosteal bone formation (42). Skin inflammation induced by the IL-17 family of cytokines has been elegantly studied in many types of IL-17 expressing models including a keratinocyte expressing IL-17C mouse model (K5-IL-17C) where keratinocyte expression of IL-17C induces a chronic skin specific inflammation (43). Taken together, these findings suggest that IL-17 is crucially involved in the pathophysiology of erosive bone disease and skin inflammation as observed in psoriatic arthritis.

Targeted Therapeutics for PsA

**TNF blockade**

TNF blockade has been successfully used to treat various autoimmune and inflammatory diseases in clinical trials. The current FDA approved TNF therapies for PsA include infliximab, etanercept, adalimumab, golimumab and certolizumab pegol. Approximately 60-70% of patients with moderate to severe psoriasis were shown to achieve a 75% improvement in Psoriasis Area and Severity Index (PASI) 75 and 40-70% of patients with active psoriasis have recently been approved for the treatment of psoriasis (53). Interestingly, the response rates of IL-17-targeted therapies in psoriasis have been successful, with moderate responses in PsA thus far, suggesting that additional variables including genetic susceptibility may be contributing to its pathogenesis. In PsA patients with mutations in TRAF3IP2 or IL23A/IL23R, it may be possible that alternative pathways may be activated or working in synergy with IL-17. Recently, others have demonstrated experimentally that Act1-deficient mice demonstrate spontaneous IL-22-dependent skin inflammation, and exposed to the IL-23/IL-17 axis, which has been demonstrated at both the clinical and basic science level (46). Interestingly, patients non-responsive to etanercept show persistent levels of serum IL-17, while responders have shown a reduction in IL-17 levels (44).

**IL-17 blockade**

Recent clinical trials with various molecules blocking IL-17 signaling have evaluated the impact of dysregulated IL-17 signaling in the pathogenesis of inflammatory diseases. Many of these studies are currently ongoing to evaluate the efficacy of anti-IL-17 and anti-IL-17R antibodies in PsO, RA, and PsA (Table 1). The biologics targeting either IL-17 or its receptor that are being studied in the setting of psoriatic disease include secukinumab, brodalumab and ixekizumab. Each one has slightly different specificities targeting the IL-17 pathway (Figure 1). Secukinumab is a fully human anti-IL-17A monoclonal antibody, ixekizumab is a humanized anti-IL-17A monoclonal antibody, while brodalumab is a fully human IL-17 receptor (IL-17RA) monoclonal antibody.

Blockade of IL-17 has resulted in remarkable success in the treatment of psoriatic disease (47). In particular, IL-17 antagonists in the setting of psoriasis have been shown to achieve higher PASI 75, 90, 100 response rates (48). In patients with plaque psoriasis, clinical trials have shown that treatment with brodalumab results in prompt clinical improvement (49). Data from Phase I-III studies has also shown that ixekizumab is highly effective in treating patients with moderate-to-severe plaque psoriasis (50-52). Similarly, use of secukinumab has produced comparable results, and both ixekizumab and secukinumab have recently been approved for the treatment of psoriasis. Interestingly, the response rates of IL-17-targeted therapies in psoriasis have been successful, with moderate responses in PsA thus far, suggesting that additional variables including genetic susceptibility may be contributing to its pathogenesis in PsA patients with mutations in TRAF3IP2 or IL23A/IL23R, it may be possible that alternative pathways may be activated or working in synergy with IL-17.
which could not be rescued by anti-IL-17 antibodies (54). Although a panoply of biologics have been summoned to combat PsA including IL-23 and IL-23R biologics that can also target the development of Th17 cells and Th17 related cytokines including IL-22 and the aforementioned TNF, the development of IL-17 and IL-17R targeted therapies are summarized below (55).

### Secukinumab

Secukinumab is a fully human IgG1k monoclonal antibody against IL-17A and is approved for the treatment of psoriasis, PsA and ankylosing spondylitis (53). Secukinumab did not reach significance in a double-blind, placebo-controlled, randomized phase IIa study, with moderate to severe PsA patients. However, there was a reduction in serum IL-17 and other cytokines with a trend of improved quality of life (59, 60). In a subsequent phase III study assessing the long-term efficacy and safety of secukinumab in patients with PsA (FUTURE II), secukinumab was significantly more effective than placebo in improving the signs and symptoms of PsA, along with patient-reported physical functioning and quality of life, with responses sustained through 52 weeks of therapy (61). These improvements were seen alongside a significant reduction in radiographic progression in the treatment group as compared to the placebo, as well as improvements in the severity of plaque and nail psoriasis in those patients with a significant concomitant psoriasis burden in addition to their joint disease (61, 62). In a similar FUTURE II study, subcutaneous weekly doses of secukinumab vs. placebo were tested instead of intravenous loading doses for the first 4 weeks, and improvements in the primary endpoint (at least 20% improvement in the ACR20 at week 24) were seen in the active arm (63, 64).

### Ixekizumab

Ixekizumab is an IL-17-targeted humanized monoclonal antibody that was studied in active PsA in a recent 24-week phase III trial (SPIRIT-P1), comparing subcutaneous ixekizumab (160 mg loading dose followed by 80 mg every two or four weeks) to subcutaneous adalimumab (40 mg every other week) or placebo in PsA patients who were naïve to biologic DMARDs (65). Significantly more patients treated with ixekizumab achieved a greater ACR20 response compared to placebo (62.1% in the q2week regimen and 57.9% in the q4), and treatment also reduced radiographic progression of joint damage. The adalimumab active reference arm also demonstrated a significantly greater ACR20 response at week 24 (57.4%) versus placebo (65). These findings are in agreement with prior studies that have shown efficacy in the setting of chronic moderate-to-severe plaque psoriasis (50). For the SPIRIT-P1 trial, an extension period of 3 years will allow for longer-term assessment of safety and efficacy.

### Brodalumab

Brodalumab is a monoclonal antibody that targets and blocks the signaling pathway of IL-17R and has been proven effective in the treatment of psoriasis (66-68). It has been evaluated in PsA patients in a placebo-controlled phase II study, which showed significant and sustained response rates (68). At week 12 of treatment, the brodalumab groups demonstrated significantly higher rates of improvement in the outcome measure, the American College of Rheumatology response criteria (ACR20), than the placebo group. Commonly reported adverse events in the brodalumab groups in the trial were upper respiratory tract infection (12%, vs. 7% for placebo), fatigue (7% vs. 4%), and diarrhea (6% vs. 4%). Concern was raised during the development of brodalumab for psoriatic disease and axial spondyloarthritis in the United States after reports of suicidal thoughts and behavior were seen in clinical trial patients taking the drug (56). Phase III trials have either been completed (AMVISION-2; NCT02024646) or terminated (AMVISION-1, NCT02029495) (56). A critical review of the trial data, however, did not reveal a causal relationship between brodalumab use and suicidality (69). Given striking results seen in psoriasis patients (66, 67), the FDA has since approved brodalumab for moderate-to-severe psoriasis with a Boxed Warning on suicidal ideation and behavior (70).

### Ustekinumab

With regards to PsA, a phase II trial showed improvements in ACR20 response rates and significant improvement in skin disease, enthesitis, dactylitis and physical functioning (77). However, there was a higher dose requirement than that used for treating psoriasis. In a phase III SUMMIT 1-2 trial, similar improvements were shown in PsA patients who were anti-TNF-experienced (78). In a SUMMIT 2 phase III trial, data through week 60 indicated that ustekinumab induces long-term significant improvement in the joint, enthesitis/dactylitis and skin symptoms of active PsA (79). These findings supported the FDA approval of ustekinumab in the treatment of active PsA as of September 2013.

### Insights and Conclusions

Psoriatic arthritis is a chronic and progressive inflammatory arthritis intimately associated with psoriasis, and can be an impairing disease that leads to reduced quality of life and significant morbidity. Treatment often requires TNF antagonists, yet many patients with PsA are not responsive to the standard anti-TNF therapies. Evidence from psoriatic lesions and synovial fluid in humans and psoriatic-like and arthritis mouse models have supported the development of therapies targeting the IL-17 pathway, which have demonstrated remarkable success in psoriasis and PsA. This is evidenced by secukinumab, the first anti-IL-17 monoclonal antibody to receive FDA approval for treatment of PsA in January 2016. The IL-23/IL-17 axis is also mechanistically relevant to PsA and an important therapeutic target as seen through the successful use of ustekinumab. Clinical trials studying other anti-IL-17 therapies and even bispacific TNF/IL-17A inhibitors are ongoing and should provide new promising insight into new therapeutic options for PsA.
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