REVIEW ARTICLE

# Shifting the focus – the primary role of IL-23 in psoriasis and other inflammatory disorders

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## Abstract

Insights into the pathophysiology of autoimmune inflammatory diseases including psoriasis have advanced considerably in recent years, and in parallel, so too have the available treatment options. Current clinical paradigms for the treatment of psoriasis have evolved to include targeted biologic therapies, starting with tumour necrosis factor-alpha (TNF-α) inhibitors and later, agents targeting interleukin (IL)-12/23 and IL-17. The most recent evidence suggests that IL-23 might be an even more potent target for the effective treatment of psoriasis and other autoimmune inflammatory disorders. This review will describe recent developments leading to the current understanding of the key role of IL-23 as a 'master regulator' of autoimmune inflammation and the clinical evidence for agents that specifically target this modulator in the context of treating psoriasis, spondyloarthropathy and inflammatory bowel disease.
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## Disclosures

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## Introduction

Psoriasis was originally believed to be a disease originating from dysregulation of keratinocyte proliferation (Fig. 1) based on histological evidence.[1,2] Through the 1980–90s, evidence pointed to psoriasis as an immune-mediated disease.[3–5] Cytotoxic T cells were identified around capillaries[3] and within the dermis and epidermis[4] of psoriatic lesions. That T-cell-targeted therapies improved psoriasis outcomes further solidified this role in the disease pathophysiology.[6,7]

Subpopulations of T cells, T helper 1 (Th1) and T helper 2 (Th2) cells were identified based on their cytokine secretory profile.[8,9] Th1 cells secrete interferon (IFN)-γ, tumour necrosis factor (TNF)-α and interleukin (IL)-2, whereas Th2 cells secrete IL-4, -5, -10 and -13.[8,9] Differentiation of naïve T cells is cytokine-dependent: IL-12 driving Th1 cell differentiation[10] and IL-2 and -4 driving Th2 differentiation.[11]

With this increased understanding, psoriasis was deemed a Th1-mediated disease, as elevated levels of TNF-α[12] and the p40
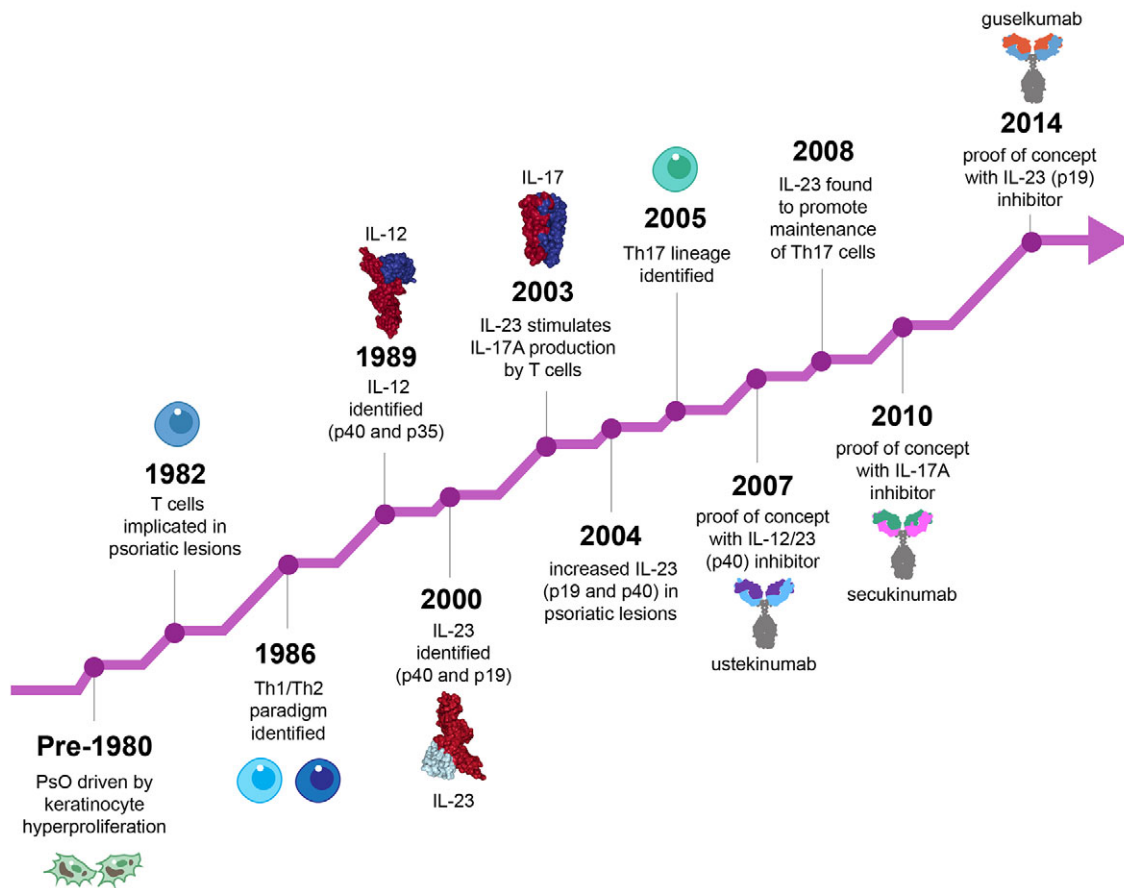
**Figure 1** Historical timeline of discoveries and evolving pathophysiologic concepts. Time (*x*-axis) not to scale. IL, interleukin; PsO, psoriasis; Th, T-helper cell.

subunit of IL-12[13] were identified in psoriatic lesions. These data supported the clinical development of TNF-α blockers as biologic treatments for psoriasis.[14]

Subsequently, IL-23 was discovered comprised of a unique p19 subunit and sharing the p40 subunit of IL-12.[15] This shared subunit suggested that IL-23, and perhaps not IL-12, could play a role in the pathogenesis of psoriasis. The p40 and p19 subunits of IL-23, but not the p35 subunit of IL-12, are elevated in multiple forms of psoriasis,[13,16,17] but not in other dermatitides,[18] highlighting the central role of IL-23 in psoriasis. Two IL-12/23p40 blockers, ustekinumab[19,20] and briakinumab,[21–23] were demonstrated more effective than placebo or etanercept, at improving symptoms of psoriasis (Psoriasis Area and Severity Index [PASI] 75 response). Although effective, the commercial development of briakinumab was terminated.[24]

## Th17 cells and the pathophysiology of autoimmune inflammation

IL-23 maintains the differentiation of naïve T cells into a distinct T-cell lineage, Th17, characterized by the secretion of pro-inflammatory IL-17 (Fig. 2).[25] IL-17 had previously been associated with animal models of inflammation,[26,27] and this led to the investigation of IL-17 inhibition in the treatment of various autoimmune diseases including psoriasis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and inflammatory bowel disease (IBD). Both Th17 cells and IL-17 are elevated in these conditions.[28] Three biologics were developed targeting IL-17 signalling: secukinumab and ixekizumab target the IL-17A isoform specifically, while brodalumab blocks the IL-17 receptor A subunit (IL-17RA) thereby blocking several cytokines from the IL-17 family.[29–31] These anti-IL-17A biologics have been shown effective in psoriasis as demonstrated by their high PASI
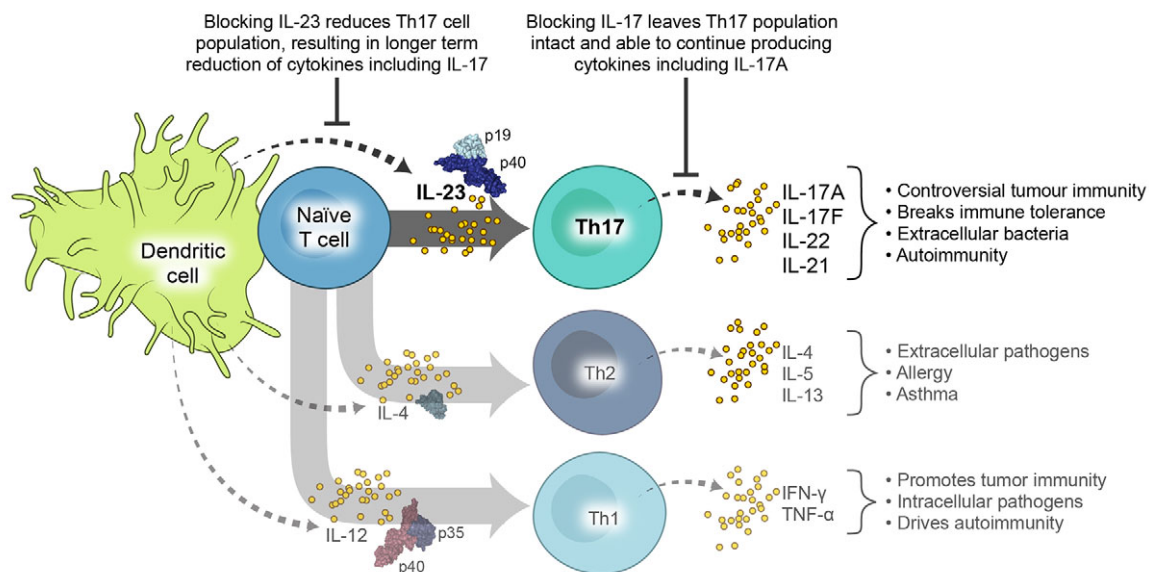
**Figure 2** Cytokine secretory profiles of T cells. Native T cells differentiate along three known pathways (Th1, Th2 and Th17) depending on the cytokine environment. These unique T-helper cells then secrete a distinct set of cytokines resulting in different physiological responses. Current psoriasis treatment approaches include blocking the cytokines produced by the differentiated T cells, or blocking the cytokines that drive pathogenic differentiation of certain T-cell lineages. IFN, interferon; IL, interleukin; Th, T-helper cell; TNF, tumour necrosis factor.

75 response rates (71–83% at 12 weeks).[29–31] Anti-IL-17A biologics have also been shown to improve symptoms of psoriatic arthritis,[32,33] ankylosing spondylitis[34] and rheumatoid arthritis.[35] In Phase II studies of patients with IBD, blocking IL-17A was ineffective. In fact, a worsening of the Crohn's disease was observed in some cases.[36,37] One hypothesis for this observation is that the gut microbiotic environment may be contributing to the pathophysiology of this disease.[36] In addition, studies have shown that IL-17 plays a role in maintenance of the intestinal epithelial barrier and in tissue repair.[38,39] A fourth IL-17 inhibitor, bimekizumab, which targets both IL-17A/F, is in early stages of clinical development.[40]

Systemic downregulation of IL-17 has been associated with adverse effects related to the key role of IL-17 in protecting the skin and mucous membranes from infection, specifically candidiasis.[41] In clinical trials, approximately 2–4% of patients treated with IL-17 blockers developed candidiasis, mostly oral infections.[41] Case reports of suicidal ideation and completed suicides have been reported in patients taking brodalumab,[42] although a recent review of the evidence suggests that this may not be directly related to the drug itself.[43] Cases of IBD flare or new onset IBD have been reported in a small proportion of psoriasis patients exposed to ixekizumab (0.29 per 100 patient-years)[44] or secukinumab (0.33 per 100 patient-years)[45] in safety

analyses of Phase II and III trials. This, coupled with the Phase II evidence of worsening of disease in patients with an established diagnosis of IBD,[36,37] has raised concerns about an association between IL-17 inhibition and IBD. However, at this time, a causal relationship has not been definitively established for IL-17 inhibitors and risk of IBD in patients with psoriasis, psoriatic arthritis or ankylosing spondylitis.[46]

## Role of IL-23 in the pathophysiology of autoimmune disorders

The differentiation of Th17 cells is activated upon exposure to transforming growth factor (TGF)-β and IL-6, resulting in the upregulation of the transcription factor retinoid-related orphan receptor (ROR)-γt.[47] (ROR)-γt promotes the expression of IL-17A and of the IL-23 receptor (IL-23R).[48] Subsequent exposure to IL-23 is required for the maintenance and expansion of the Th17 lineage.[26,49,50] In the absence of IL-23, the Th17 phenotype is lost.[49] IL-23 is produced by antigen-presenting Langerhans cells,[51] dendritic cells[52] and monocytes/macrophages[53] of the innate immune system in response to an inflammatory or biochemical insult, specifically at barrier sites such as the skin, gut and entheses. Binding of IL-23 to its receptor initiates a signalling cascade phosphorylating and activating Jak2 and STAT3,[54] ultimately leading to increased expression of IL-17 and

ROR-γt.[55] Together, these observations highlight the fundamental role of IL-23 in the production of IL-17.

Given the essential role of IL-23 in maintaining pathogenic Th17 cell populations, blocking IL-23 could be safer and more effective therapeutic target. Blocking IL-23 decreases levels of circulating IL-17A, likely due to a reduction in the number and/or activity of pathogenic Th17 cells.[56] However, IL-17 is not completely eliminated, possibly because other cells produce IL-17 independent of IL-23 stimulation.[41,57,58] IL-23 bridges the innate and adaptive immune system in that it can stimulate IL-17 production from natural killer cells and neutrophils to control an acute infection (innate) and from T cells leading to an inflammatory autoimmune response (adaptive).[59] Therefore, a response to candida infection or other barrier insult can still be mounted in the setting of IL-23 blockade.[41,57,58]

Selectively blocking the IL-23 subunit p19 also has potential benefits over blocking the p40 subunit shared by IL-23 and IL-12. IL-12 is essential for driving Th1 differentiation and therefore the immune response to infectious pathogens.[10,60] Many host defense processes can function if IL-12 remains intact even when IL-23 is blocked.[61] As Th1 cells secrete IFN-γ, these cells can also decrease the effects of IL-23 by downregulating the IL-23 receptor and further reducing Th17 differentiation.[62]

Targeting IL-23 instead of TNF-α may also confer a benefit in terms of risk of tuberculosis or hepatitis reactivation, as well as 'paradoxical psoriasis' or psoriasiform eruption.[63] It has been speculated that paradoxical psoriasis arises from a cytokine imbalance that favours dendritic cell activation and the unopposed production of IFN-α.[63,64] Increased IFN-α causes upregulation of the chemokine receptor CXCR3 in Th1 cells, which could induce migration to the psoriatic lesion.[63]

## IL-23: The 'master regulator' in psoriasis, spondyloarthropathy and inflammatory bowel disease

While there is considerable evidence that IL-23 may be a key regulator in autoimmune conditions in general, primary research supports a role for IL-23 in the pathophysiology of psoriasis specifically. Rodent models have shown that injection of IL-23 into healthy mice resulted in psoriasis-like lesions.[65] Conversely, p19 knock-out mice are protected against imiquimod-induced psoriasis, suggesting that blocking IL-23 could prevent the development of the disease.[66] Similarly, single nucleotide polymorphisms (SNPs) in the genes expressing the p40 subunit of IL-12/23 or the IL-23 receptor can confer either protection against[67] or susceptibility to[68,69] the development of psoriasis in humans (Fig. 3).

A growing body of the literature supports a central role of IL-23 in the pathophysiology of spondyloarthropathy. Cells harbouring IL-23 receptors have been identified in the entheses and have been shown to induce the production of pro-inflammatory IL-17.[70] In a murine model, administration of IL-23 resulted in enthesal inflammatory arthritis and bone erosion similar to spondyloarthritis.[71] The same gene polymorphisms in the IL-23 receptor associated with psoriasis have been shown to be associated with psoriatic arthritis[72] and ankylosing spondylitis.[73]

Murine IBD models have shown that IL-23 is a requirement for the induction of intestinal mucosal inflammation.[74] Elevated transcription of IL-23 has been found in the inflamed mucosa of patients with Crohn's disease, with a dose-dependent effect on disease severity.[75] Studies suggest that blocking IL-23 does not impair IL-17 production by innate non-T-cell lymphocytes[76] thereby preserving intestinal epithelial integrity and tissue repair mechanisms.[38,39]

These data support a unifying aspect of IL-23 in the pathophysiology of autoinflammatory diseases and suggest that targeting IL-23 may present a common approach to the treatment of diseases including psoriasis, IBD and spondyloarthropathy which are often overlapping (Fig. 4).[77]

## Clinical data support a principal role for IL-23 in psoriasis

Understanding the pathophysiology of disease may identify therapeutic targets. Conversely, the clinical application of targeted therapies provides information about the mechanisms underlying disease. The clinical development of anti-IL-23p19 drugs for psoriasis will be described below.

### Guselkumab

A Phase I study examined the safety, efficacy and biomarker response of a single dose of guselkumab in 24 patients with psoriasis.[56] Blocking IL-23 modulated the expression of several genes in psoriatic skin lesions including IL-17A, IL-17F and CXCL1 with limited effects on the Th1 pathway and decreased levels of circulating IL-17A, likely due to a reduction in the number and/or activity of pathogenic Th17 cells. Reductions in levels of other cytokines including IL-17F, IL-22 and TNF-α did not reach statistical significance.

In a Phase II study, varying doses of guselkumab (i.e. 5, 15, 50, 100 and 200 mg) were compared to placebo (weeks 0–16) and to adalimumab (weeks 0–52).[78] For all efficacy measures, dose–response improvements in the guselkumab-treated groups were greater than placebo.[78] Clinical improvements in the guselkumab-treated groups peaked at ~20 weeks and were maintained through 40 weeks.[78] The incidence of adverse effects was low, with similar rates of infection in the placebo, guselkumab and adalimumab arms. The VOYAGE-1 Phase III trial confirmed the superiority of guselkumab over placebo and adalimumab (PASI 90 response rates 73.3%, 2.9% and 49.7%, respectively).[79] Adverse event rates in this trial were also similar between treatment groups.[79] In VOYAGE-2, adalimumab non-responders (not achieving PASI 90 by week 24) were switched to guselkumab at week 28.[80] After 48 weeks of treatment, 66.1% of adalimumab non-responders treated with guselkumab achieved
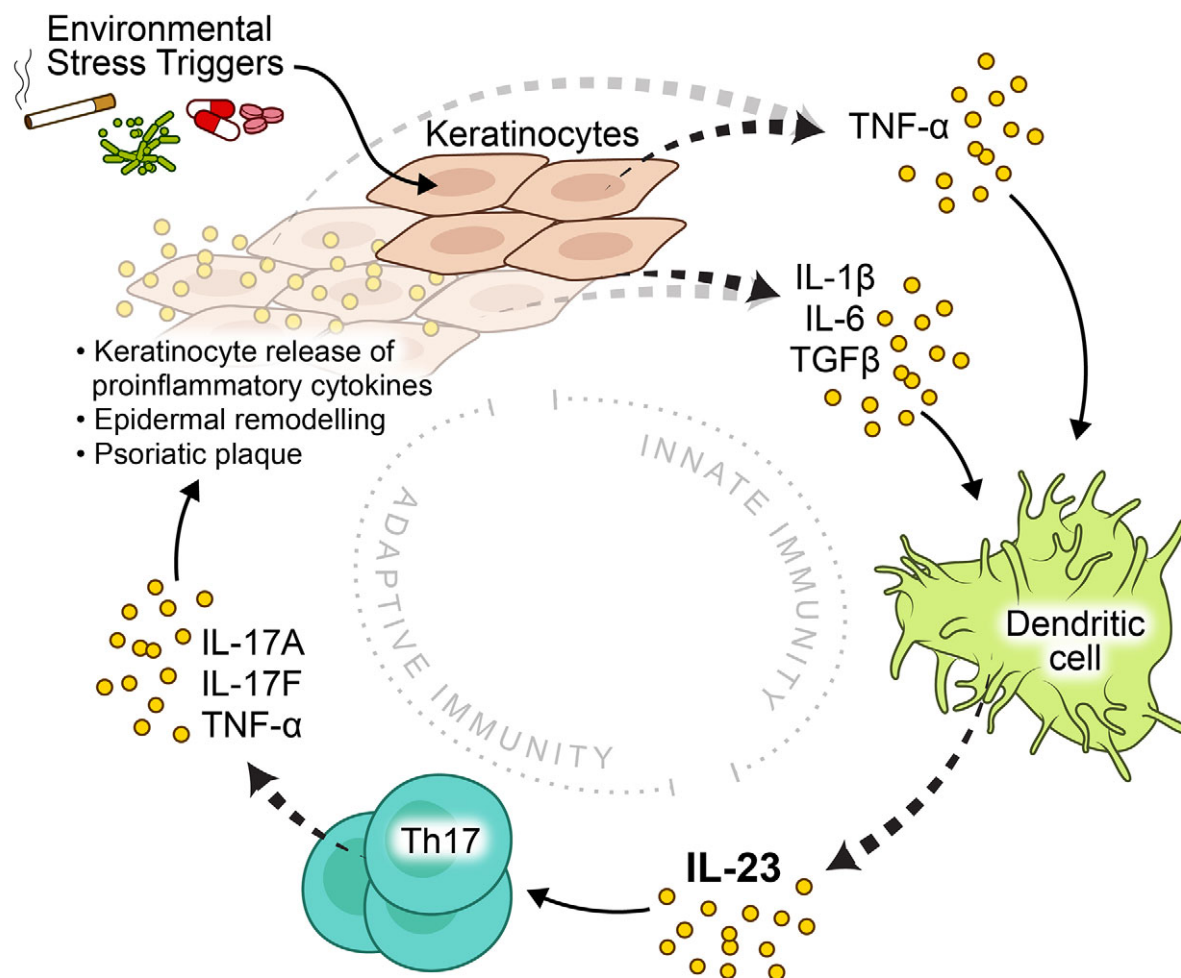
**Figure 3** Current model of the pathophysiology of psoriasis. IL-23 bridges the innate and adaptive immune responses and plays a key role in inducing Th17 cell differentiation. The resulting elevated IL-17 secretion maintains the pathological response of keratinocytes, resulting in psoriatic plaque formation. IL, interleukin; Th, T-helper cell; TGF, transforming growth factor; TNF, tumour necrosis factor.

a PASI 90 response and 28.6% achieved PASI 100.[80] In NAVI-GATE, guselkumab demonstrated superiority over the IL-12/23 inhibitor, ustekinumab, in patients who failed to respond to ustekinumab compared to those who remained on ustekinumab (51.1% vs. 24.1% of patients with PASI 90 at week 52; $P < 0.001$).[81] Guselkumab has been shown to reduce IL-17 levels in blood and psoriatic lesions, supporting a causal relation between a reduction in the number, or activity, of Th17 cells and clinical improvements in psoriasis.[56]

### Tildrakizumab

In a Phase IIb trial, tildrakizumab 5, 25, 100 and 200 mg was compared to placebo for 52 weeks.[82] The PASI 75 response rate (primary endpoint) was significantly higher in tildrakizumab-treated patients compared to placebo by week 16 (33–74% compared to 4% for placebo; $P < 0.001$ vs. placebo for all doses) and was generally maintained through 52 weeks.[82] PASI 90 rates were 12–52% at week 16, and 73–81% of week 16 responders maintained PASI 90 at week 52.[82] Adverse events were similar between active treatment and placebo groups.[82] The Phase III trial, reSUR-FACE-1, confirmed these results (PASI 75 response rates ranged from 62% to 64% at week 12 and 80% to 82% at week 28).[83] In reSURFACE-2, 37–39% of patients treated with tildrakizumab achieved PASI 90 at 28 weeks compared to 21% with etanercept and 1% with placebo.[83] Adverse events were similarly low between tildrakizumab and etanercept.[83]
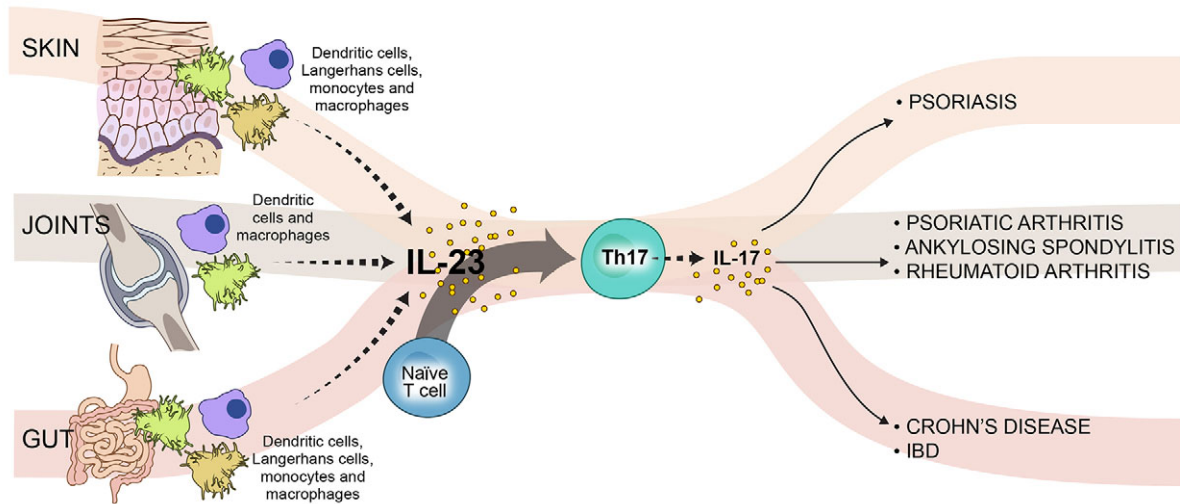
**Figure 4** Unifying concept of IL-23 as a 'master regulator' in the pathogenesis of autoimmune disorders. Psoriasis, rheumatoid diseases and inflammatory bowel disease are all characterized by the pathogenic overproduction of IL-23 at barrier sites, i.e. the skin, the joints and the gut, respectively. This makes IL-23 an attractive target for all three conditions. IBD, inflammatory bowel disease; IL, interleukin; Th, T-helper cell.

### Risankizumab

In a Phase I trial, PASI 75, 90 and 100 response rates were significantly higher in the risankizumab group compared to placebo at 12 weeks (87%, 58%, 16% and 0%, respectively), and responses were maintained through 24 weeks.[84] Adverse events were not different between treatment and placebo groups.[84] Significant reductions in IL-23, IL-23R and IL-17 were demonstrated in lesional skin biopsies with active treatment compared to control.[85] In a Phase II trial, risankizumab was superior to ustekinumab in the proportion of patients achieving PASI 90 (77% vs. 40%; $P < 0.001$ pooled risankizumab groups vs. ustekinumab).[85] Adverse events were similar between treatments.[85] Expression of the IL-23 receptor was shown to be downregulated in the risankizumab-treated group but not in patients treated with ustekinumab. Levels of downstream IL-17 were not reported.[85]

### Benefits of reducing Th17 clonal expansion with IL-23 blockers

There is clear clinical evidence that specific IL-23p19 blockade is effective, safe and superior to other biologics that act on downstream cytokines of the IL-23/Th17 pathway. A potential benefit of reducing the clonal expansion of Th17 cells via IL-23 inhibition is low dosing frequency and a sustained drug effect. After induction, IL-23 blockers are effective when dosed every 8–12 weeks compared to every 2 weeks for adalimumab[78] or 4 weeks for IL-17 blockers. A single dose of 18 mg of risankizumab

resulted in a 53% PASI 75 and 28% PASI 90 response rate.[85] At higher doses of risankizumab, PASI 75 and 90 response rates generally persisted for up to 32 weeks following the final treatment.[85] In a randomized withdrawal study of guselkumab, PASI 90 response rates began to diverge from patients who continued maintenance treatment around week 32.[80] It is postulated that blocking IL-23 may be more effective and the effects longer lasting due to an upstream effect including reduced expression of several downstream pro-inflammatory cytokines secreted by Th17 cells (e.g. IL-17A, IL-17F, IL-21 and IL-22).[86] This could be due to impaired survival or a phenotypic change in the pathogenic Th17 cells, or a restoration of altered T-reg function:[86] important as Th17 cells are long-lived and metabolically active, even after skin healing.[87,88] Preventing initial production of these cells could prove beneficial.

### Evidence for role of IL-23 in other disease states

An accumulating body of evidence suggests that the benefits of IL-23 blockade are not limited to psoriasis as IL-23 and IL-12/23 blockers have been investigated in clinical trials for various other inflammatory diseases.[89] Clinical data in the investigation of rheumatoid diseases (i.e. psoriatic arthritis, ankylosing spondylitis and rheumatoid arthritis) have reported varying results. Significant improvements in symptoms, physical function and quality of life were observed with guselkumab in psoriatic arthritis patients.[90] Ustekinumab reduced signs and symptoms of ankylosing spondylitis in a proof-of-concept study.[91] In contrast,

neither ustekinumab nor guselkumab was effective at reducing signs and symptoms of active rheumatoid arthritis.[92]

Mixed results have also been reported in other inflammatory diseases. Ustekinumab, risankizumab and MEDI2070 (anti-p19 monoclonal antibody) have demonstrated effectiveness for the treatment of Crohn's disease.[93–95] Ustekinumab was not effective in treating symptoms of multiple sclerosis, although it was well tolerated.[96]

## Conclusions

Psoriasis is recognized as a Th17-mediated inflammatory disorder. A growing body of evidence supports IL-23 as the 'master regulator' of the immune-inflammatory response in psoriasis and other inflammatory disorders due to its critical role in maintaining the population of cytotoxic Th17 cells that produce pro-inflammatory cytokines including IL-17 and IL-22. Emerging results of randomized clinical trials suggest that selectively blocking IL-23 (p19 subunit) offers benefits above and beyond current treatment strategies for psoriasis producing high levels of efficacy, a favourable safety/tolerability profile, and the convenience of infrequent dosing. IL-23 blockers represent an important step forward in the continued evolution of the treatment landscape. Patients with psoriasis and other inflammatory diseases can expect better outcomes as therapies become more targeted and refined.

## Acknowledgements

## Source of Molecular Data for Illustrated Figures

Molecular images were drawn based on molecular data viewed using NGL Viewer software and based on the following research: Image of **1F45** (C. Yoon, S.C. Johnston, J. Tang, J.F. Tobin, W.S. Somers (2000) human interleukin-12 *Embo J.* 19: 3530–3541), **4HR9** (S. Liu, X. Song, B.A. Chrunyk, S. Shanker, L.R. Hoth, E.S. Marr, M.C. Griffor (2013) human interleukin 17A *Nat Commun* 4: 1888–1888), **3D87** (B.M. Beyer, R. Ingram, L. Ramanathan, P. Reichert, H.V. Le, V. Madison, P. Orth (2008) crystal structure of Interleukin-23 *J.Mol.Biol.* 382: 942–955) and **3HMW** (J. Luo, S.J. Wu, E.R. Lacy, Y. Orlovsky, A. Baker, A. Teplyakov, G. Obmolova, G.A. Heavner, H.T. Richter, J. Benson (2010) crystal structure of ustekinumab FAB *J.Mol.Biol.* 402: 797–812) created with NGL (A.S. Rose, A.R. Bradley, Y. Valasatava, J.M. Duarte, A. Prlić, P.W. Rose (2016) Web-based molecular graphics for large complexes. ACM Proceedings of the 21st International Conference on Web3D Technology (Web3D '16): 185–186; A.S. Rose, P.W. Hildebrand (2015) NGL Viewer: a web application for molecular visualization. *Nucl Acids Res* (1 July 2015) 43 (W1): W576–W579 first published online April 29, 2015).

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