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IL-12 and IL-23 pathway inhibition in inflammatory bowel disease

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

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Abstract

Interleukin-12 (IL-12) and interleukin-23 (IL-23), which belong to the IL-12 family of cytokines, have a key role in intestinal homeostasis and inflammation and are implicated in the pathogenesis of inflammatory bowel disease. Upon their secretion by antigen-presenting cells, they exert both pro-inflammatory and anti-inflammatory receptor-mediated effects. An increased understanding of these biological effects, particularly the pro-inflammatory effects mediated by IL-12 and IL-23, has led to the development of monoclonal antibodies that target a subunit common to IL-12 and IL-23 (p40; targeted by ustekinumab and briakinumab), or the IL-23-specific subunit (p19; targeted by risankizumab, guselkumab, brazikumab and mirikizumab). This Review provides a summary of the biology of the IL-12 family cytokines IL-12 and IL-23, discusses the role of these cytokines in intestinal homeostasis and inflammation, and highlights IL-12- and IL-23-directed drug development for the treatment of Crohn's disease and ulcerative colitis.

Introduction

Inflammatory bowel disease (IBD) is a complex gastrointestinal disorder arising from an inappropriate immune reaction against environmental factors, including gut microbiota, in genetically susceptible individuals[1]. A growing understanding of the underlying disease pathogenesis has resulted in the development of agents that target inflammatory components of the disease process, which has revolutionized IBD care[2]. For over a decade, the principal target of monoclonal antibodies in IBD was tumour necrosis factor (TNF). Despite the revolutionary nature of TNF inhibitors, 10–30% of patients in clinical trials and practice do not respond, and 23–46% require dose intensification beyond 12 weeks of therapy, a surrogate for loss-of-response to these agents[3]. Agents with novel modes of action were therefore required for treatment of IBD. The discovery of the interleukin-23 (IL-23) receptor (encoded by *IL23R)* as an IBD susceptibility locus[4] and of the importance of the IL-12 family of cytokines in intestinal inflammation led to the development of biological agents that target IL-12 and/or IL-23 (ref. 5). This Review focuses on the IL-12 family cytokines IL-12 and IL-23, discussing their role in intestinal homeostasis and inflammation — including in IBD — and highlighting drug development related to the IL-12 and IL-23 axes.

IL-12 and IL-23 cytokine biology

IL-12 is comprised of two protein subunits, p40 and p35, linked by a disulfide bond. Initially discovered over 30 years ago as a protein released by a human lymphoblastoid cell line and capable of activating interferon-γ (IFNγ) production by natural killer (NK) cells and T cells, a clear role for IL-12 in driving T helper 1 (T_H1) cell responses was subsequently established[6–9].

IL-23 was identified a decade after the discovery of IL-12 (ref. 10). Phenotypic differences between mice deficient for either the IL-12 p40 or p35 subunit, specifically in their ability to clear bacterial infections[10,11], led to the hypothesis that p40 might pair with subunits other than p35 to exert its antimicrobial effects. A sequence database search for homologues to p35 identified p19 as a protein that associated with p40 and formed the unique cytokine IL-23 (ref. 10). In contrast to IL-12, IL-23 was first described as having an effect on memory T cells but not on naive T cells[10]. Subsequently, IL-23 was shown to promote expansion and maintenance, but not differentiation, of T helper 17 (T_H17) cells[12]. These effector T cells, which are characterized by production of IL-17A, IL-17F, IL-22, IL-26, TNF and in some cases IFNγ, are involved in immune responses to bacteria and fungi and have been recognized as key mediators in autoimmunity[13].

Both IL-12 (p35 and p40) and IL-23 (p19 and p40) are produced by antigen-presenting cells (APCs), including dendritic cells and macro phages, in response to early innate signals[14,15] (Figs. 1 and 2). IL-12 production by dendritic cells is also driven by the CD40 ligand on T cells[16] and is modulated by cytokines such as IFNγ, IL-18, granulocyte–macrophage colony-stimulating factor (GM-CSF), IL-4 and by IL-12 itself[15,17,18]. Signals that also promote IL-12 production (including CD40 stimulation), certain cytokines, and bacteria or viruses can lead to production of IL-23 by APCs[19–21]. Studies support the ability of intestinal epithelial cells (IECs) to produce monomeric IL-23p19 under inflammatory and mitogenic signals[22]. Secretion of IL-23 by IECs has also been reported in a murine model of colitis[23].

The biological effects of IL-12 and IL-23 are receptor-mediated. The IL-12 receptor (IL-12R) is comprised of two chains, IL-12Rβ1 and IL-12Rβ2, that bind to p40 and p35, respectively[24] (Fig. 1). In addition to its well known expression on lymphoid cells, IL-12R is also expressed by macrophages and dendritic cells[25,26]. Whereas the IL-23 p40 subunit also binds to IL-12Rβ1, the p19 subunit associates with the IL-23R chain to drive intracellular signalling mediated by IL-23 (ref. 27) (Fig. 2). In addition to lymphoid cells (specifically, T cells and type 3 innate lymphoid cells (ILC3s)), IL-23R is also found on monocytes, macrophages and dendritic cells[27,28]. The IL-23R chain is not expressed by naive T cells, and IL-23, in contrast to IL-12, preferentially activates memory T cells[10,29]. In T cells, IL-23R is expressed in response to induction of the retinoid-related orphan receptor-γt (RORγt)-dependent transcriptional activity[30].

Both IL-12 and IL-23 receptors are associated with and activate tyrosine kinase 2 (TYK2) and Janus kinase 2 (JAK2); however, receptor-mediated signalling occurs via distinct pathways that lead to independent immunological responses[24,31] (Figs. 1 and 2). In vitro

studies using cells derived from humans and mice have demonstrated that the signal transducer and activator of transcription (STAT) family members STAT1, STAT3, STAT4 and STAT5 can all be phosphorylated in response to binding of IL-12 and IL-23 to their receptors, although STAT4 is predominantly phosphorylated in response to IL-12 receptor binding[32], and IL-23 responses are mediated predominantly by STAT3-dependent signalling[27,33]. However, the relative contribution of the different STAT family members in IL-12- and IL-23-mediated signalling can vary in different cell types[34].

IL-12, IL-23 and gut homeostasis

Constitutive IL-12/IL-23 p40 promoter activity and IL-23p19 protein expression has been detected in the terminal ileum of unchallenged mice, suggesting that the small intestine is a critical, functionally relevant location for these cytokines under homeostatic conditions[35]. Production of IL-12 and IL-23 by APCs seems to be mainly triggered by Toll-like receptor signalling in the antigen-rich reservoir of the gut[34,36,37]. Stimulation of IL-12R on APCs promotes T cell activation[26,38] and antibacterial responses[39,40], and IL-23 has been shown to promote cytokine secretion and antimicrobial responses in human macrophages[34,41] (Table 1). Hence, both IL-12 and IL-23 can shape immune responses independent of their activation of IFNγ and IL-17 responses[42].

T_H17 cells, a subset of T cells, are also present in the small intestine under homeostatic conditions[43], where they have been shown in mouse and human studies to undergo IL-23-mediated activation[44–46], produce IL-17A and IL-17F, and exert inflammatory effects upon antigen challenge. This cell subset can also have an immunosuppressive function under homeostatic conditions, and in this case are referred to as regulatory T_H17 cells[43]. IL-17A exerts direct effects on gut IECs by controlling the production of tight junction proteins and molecules that limit permeability of the epithelial barrier and preserve gut barrier function in vivo[47]. In mice, loss of the IL-17R adaptor protein, ACT1, suppressed these IL-17A protective effects, and γδ T cells were identified as a source of IL-23-independent IL-17A production in this setting[47]. In addition, mice deficient for IL-17 (*Il17*$^{-/-}$) and those with a conditional deletion of the IL-17R adaptor protein ACT1 in epithelial cells had diminished colonic barrier function[48]. These findings might at least partially explain the lack of efficacy of the anti-IL-17 antibody secukinumab in patients with Crohn's disease[49].

IL-23 stimulation of colonic ILC3 cells activates STAT5 and the production of IL-22, a cytokine that is crucial for STAT3 activation in IECs and that has been associated with mucosal healing in mouse models of colitis[50–52]. Although ILC3 cells can produce T_H17 cytokines, such as IL-17A and IL-22 (refs. 53,54), and belong to the lymphoid lineage, they lack $CD3^+$ T cell receptors on their surface and are therefore activated via T cell-receptor-independent mechanisms. Gut-resident CX_3CR1^+ macrophages have been implicated as important sources of IL-23-dependent ILC3 activation, and IL-23 can cooperate with other cytokines to activate ILC3s[55–57]. Conditional knockout mice carrying a deletion in *IL23R* specifically in IECs have attenuated mucosal IL-22 mRNA levels and exhibit dysbiosis[52].

Although a role for IL-23 in mucosal homeostasis is evident, a functional role for IL-12, which is a well established inducer of mucosal T_H1 cell responses and IFNγ production, in

the healthy intestine is less well understood. Interestingly, mice deficient in IL-12 p35 or p40 do not display spontaneous gut pathology, which potentially supports the concept that IL-12 is not essential to maintain homeostatic conditions in the intestine[58,59].

IL-12, IL-23 and IBD

Multiple different genes within the IL-23–T_H17 pathway have been associated with altered risk for both Crohn's disease and ulcerative colitis. The most notable of these associations is a variant of *IL23R* that reduces risk of development of IBD by approximately two-fold in individuals of European ancestry[4]. The *IL23R*^{R381Q} protective variant results in a loss-of-function of IL-23R, with reduced STAT3 signalling and T_H17-mediated cell responses upon exposure to IL-23 (refs. 60–62). Studies have demonstrated that in human macrophages, autocrine and/or paracrine IL-23 promotes secretion of multiple other inflammatory cytokines (TNF, IL-1β, IL-6, IL-8 and IL-10)[34], thereby providing another mechanism through which IL-23 might be contributing to intestinal inflammation. The IBD protective *IL23R*^{R381Q} variant leads to a reduction of these cytokines in macrophages[34]. Interestingly, the capacity of IL-23 to induce responses in human macrophages requires dynamic recycling of IL-23R[34], which might have implications when designing certain therapeutic approaches. There are multiple splice forms of IL-23R, and some[63] but not all studies[34] have shown that the *IL23R*^{R381Q} variant results in increased expression of soluble IL-23R, which could then function as a decoy to reduce IL-23 responses. In addition, some in vitro studies have shown reduced protein stability of the *IL23R*^{R381Q} variant[64], whereas another has not[34]. Multiple other common and rare IBD genetic associations in the *IL23R* gene region have been identified[4,65,66]. In some cases, studies have gone on to examine mechanisms by which specific non-coding variants modulate IL-23R expression[67]. Notably, there is substantial heterogeneity in the *IL23R* gene across ancestries (for example, East Asian compared with European)[68–70]. Variants in regions containing genes that are associated with the IL-23 and T_H17 cell pathways and that confer altered risk for IBD have also been identified, including variants in the cytokine subunits (*IL12B* (the p40 subunit)), signalling pathways (*JAK2*, *TYK2*, *STAT3*/*STAT5*, *STAT4*), transcription factors (*RORC*) and cell surface molecules (*CCR6*)[66,71]. Taken together, these genetic associations further highlight the importance of the IL-23–T_H17 pathway in IBD pathogenesis.

As previously mentioned, the IL-12 and IL-23 pathways are important in host defence. Consistent with the loss-of-function phenotype, macrophages from *IL23R*^{R381Q} IBD-protected carriers demonstrate less effective microbial clearance relative to macrophages from wild-type homozygous (*IL23R*$^{R381/R381}$) carriers[41]. Although a higher overall risk of infection in *IL23R*^{R381Q} carriers has not yet been demonstrated, one study reported an increased frequency of active pulmonary tuberculosis[72], suggesting that *IL23R*^{R381Q} carriers might be at greater risk of infection in regions with endemic tuberculosis. Another study found increased intestinal microbial diversity and richness, and increased frequency of select phylotypes, in *IL23R*^{R381Q} carriers[73], which might also theoretically contribute mechanistically to protection from development of Crohn's disease.

The benefits of either blockade or deletion of the shared IL-12 and IL-23 p40 subunit in reducing intestinal inflammation have been demonstrated in multiple models

of experimental colitis (for example, *IL10*$^{-/-}$, adoptive T cell transfer, and 2,4,6-trinitrobenzenesulfonic acid)[37,74–77]. IL-12 expression is elevated in lamina propria mononuclear cells from patients with Crohn's disease, and IL-12 can then promote lamina propria T cell inflammatory responses[78,79]. The results of p40 blockade in experimental animal studies have been corroborated in human studies. Reduced intestinal lamina propria inflammatory cytokines (IL-12p70, IL-23, IFNγ and TNF), including those expressed by T cells (IL-17 and IL-6) were found in patients with Crohn's disease treated with antibodies targeting the shared p40 subunit compared with patients treated with placebo[80], and a concentration-dependent reduction in the frequency of circulating T follicular helper cells has also been observed in patients with Crohn's disease treated with antibodies to the shared p40 subunit[81].

A clear role for IL-23 in promoting intestinal inflammation has also been demonstrated. Transgenic expression of IL-23p19 in mice results in severe intestinal inflammation[82]. On the other hand, blockade or deletion of either IL-23p19 (and not IL-12p35) or IL-23R in experimental models of colitis reduces inflammation[37,76,83,84]. It is presumed that this occurs because of a reduction in pathogenic T_H17 cells. However, IL-23 can also promote inflammation through T_H17-cell-independent mechanisms, including reducing regulatory T cells and increasing ILC3 responses[85,86]. Environmental factors (for example, food dyes) can also contribute to IL-23-driven intestinal inflammation[87,88]. In vivo studies have shown that while IL-12/IL-23p40 and IL-23p19 can lead to similar degrees of local intestinal inflammation in experimental models of colitis, IL-12/IL-23p40 may preferentially contribute to systemic immune activation[48,76,77]. Another study has shown that these two cytokines can act in a temporally sequential biphasic manner. Eftychi et al. demonstrated in mice that develop spontaneous colitis triggered by death of IECs that IL-12 promoted inflammation in response to intestinal epithelial barrier damage and exposure to bacteria in the early stages of disease, and that IL-23-dependent responses drove more chronic pathology as the mice aged[89].

As previously described, IL-23 can mediate different roles in distinct cell subsets in the intestine. As such, IL-23 can mediate both inflammatory (via pathogenic T_H17 cells, innate lymphoid cells and macrophages)[85] and protective (epithelial cells, antimicrobial pathways and downregulation of T_H1 cells)[52,90–92] effects, which might have implications for different responses among patients to therapeutic blockade of this pathway. An increased understanding of the various effects of IL-23 and IL-12 (for example, cell-specific regulation, kinetics and immunological context) might ultimately enable improved design of therapeutic targeting.

IL-12- and IL-23-directed therapy for IBD

Drugs targeting IL-12/IL-23 currently approved or in clinical development for the treatment of IBD are fully human monoclonal antibodies directed against either the p40 subunit (ustekinumab and briakinumab) common to IL-12 and IL-23, or the IL-23-specific p19 subunit (risankizumab, guselkumab, brazikumab and mirikizumab). Designs and outcomes for trials representing the latest phase of clinical development for these agents are detailed in

Supplementary Tables 1 and 2 and briefly summarized below. Recently published subgroup and/or post hoc analyses are also described below.

Moderate-to-severe Crohn's disease

Ustekinumab.—Ustekinumab was approved for the treatment of moderate-to-severe Crohn's disease on the basis of the UNITI induction (UNITI-1 and UNITI-2) and maintenance (IM-UNITI) trials[93] (Supplementary Table 1). A substudy of the UNITI trials evaluated the efficacy of ustekinumab in inducing and maintaining endoscopic healing[94]. The primary outcome, mean change from baseline in the Simple Endoscopic Score for Crohn's Disease (SES-CD), was significantly greater at week 8 in patients treated with ustekinumab ($n = 155$) compared with patients treated with placebo ($n = 97$) (−2.8 versus −0.7, $P = 0.012$). Although the mean change in SES-CD was numerically greater at week 44 with ustekinumab, it was not significantly greater than placebo (−2.5 versus −1.9, $P = 0.176$)[94]. Histological outcomes were also assessed using data from the UNITI programme. A significant reduction in the mean Global Histologic Disease Activity Score (GHAS) from baseline to week 8 was observed with ustekinumab (10.4 ± 7.0 to 7.1 ± 5.9, $P < 0.001$), but not with placebo (from 9.2 ± 6.4 to 7.8 ± 6.2, $P = 0.193$); the reduction in overall GHAS among those receiving ustekinumab and placebo was similar at week 44 (ref. 95).

The phase III SEAVUE trial[96] was a randomized head-to-head trial of ustekinumab (~6 mg kg^{-1} intravenously at baseline followed by 90 mg subcutaneously every 8 weeks; $n = 191$) or adalimumab (160 mg and 80 mg subcutaneously at baseline and week 2, respectively, followed by 40 mg subcutaneously every 2 weeks; $n = 195$) for patients naive to treatment with biologics. The primary endpoint, clinical remission (Crohn's Disease Activity Index (CDAI) score <150) at week 52, was achieved by 65% of patients treated with ustekinumab and 61% of patients treated with adalimumab (difference = 4.0%; 95% CI −5.5% to 13.5%; $P = 0.417$)[96]. Endoscopic response and remission rates were not statistically different at week 52 (Supplementary Table 1).

The efficacy of ustekinumab using either a treat-to-target or standard-of-care (dose frequency based on European Union summary of product characteristics (every 8 or 12 weeks)) strategy was explored in the phase IIIb STARDUST study. Patients who achieved a 70-point reduction in baseline CDAI score at week 16 with ustekinumab induction therapy (single 6 mg kg^{-1} intravenous dose at week 0 followed by 90 mg subcutaneously at week 8) were randomized into the treat-to-target ($n = 220$) or standard-of-care ($n = 221$) groups. Similar proportions of patients achieved the primary outcome of endoscopic response (≥50% reduction in SES-CD score from baseline) at week 48 using a treat-to-target or standard-of-care strategy (37.7% versus 29.9%, $P = 0.0933$; non-responder imputation)[97].

Risankizumab.—Risankizumab was approved for the treatment of moderate-to-severe Crohn's disease by the US Food and Drug Administration (FDA) on the basis of the results of three pivotal phase III trials (ADVANCE[98] and MOTIVATE[98] (induction) and FORTIFY[99] (maintenance)). Treatment with risankizumab (600 mg or 1,200 mg intravenously) at weeks 0, 4 and 8 was significantly superior to placebo for the co-primary outcome of clinical remission (CDAI <150 for sites in the USA; average daily stool

frequency ≤2.8 and abdominal pain ≤1 and not worse than baseline for sites in locations other than the USA) and endoscopic response (decrease in SES-CD >50% from baseline or ≥2-point reduction from baseline in SES-CD score for patients with isolated ileal disease and baseline SES-CD ≥4) at week 12 in both the ADVANCE (CDAI remission: 600 mg, 45% (152/336); 1,200 mg, 42% (141/339); placebo, 25% (43/175); stool frequency and abdominal pain score clinical remission: 600 mg, 43% (146/336); 1,200 mg, 41% (139/339); placebo, 22% (38/175); and endoscopic response: 600 mg, 40% (135/336); 1,200 mg, 32% (109/339); placebo, 12% (21/175)) and MOTIVATE induction studies (CDAI remission: 600 mg, 42% (80/191), 1,200 mg, 40% (77/191); placebo, 20% (37/187); stool frequency and abdominal pain score clinical remission: 600 mg, 35% (66/191); 1,200 mg, 40% (76/191); placebo, 19% (36/187); and endoscopic response: 600 mg, 29% (55/191); 1,200 mg, 34% (65/191); placebo, 11% (21/187))[98], with no apparent benefit to higher doses observed with short-term treatment (Supplementary Table 1). Patients who responded to 12 weeks of risankizumab induction therapy in ADVANCE and MOTIVATE were re-randomized to subcutaneous treatment with 180 mg or 360 mg risankizumab, or placebo, every 8 weeks[99]. The proportion of patients achieving the co-primary endpoint of clinical remission and endoscopic response (both outcomes as defined previously) at 52 weeks was significantly higher compared with placebo in the risankizumab 360-mg group (CDAI remission: 52% (74/141) versus 41% (67/164) for placebo; stool frequency and abdominal pain score clinical remission: 52% (73/141) versus 40% (65/164) for placebo; and endoscopic response: 47% (66/141) versus 22% (36/164) for placebo), whereas risankizumab 180 mg was significantly superior to placebo for the outcomes of CDAI < 150 remission (55% (87/157) versus 41% (67/164)) and endoscopic response (47% (74/157) versus 22% (36/164))[99] (Supplementary Table 1). Importantly, both risankizumab doses were significantly superior to placebo for the outcomes of endoscopic remission (SES-CD ≤4 and ≥2 point reduction versus baseline with no individual subscore greater than 1) and deep remission (CDAI < 150 and endoscopic remission) at week 52 (ref. 99) (Supplementary Table 1).

Endoscopic outcomes in response to risankizumab induction and maintenance treatment were numerically higher in patients who were intolerant to or had an inadequate response to conventional therapies (aminosalicylates, oral locally acting steroids, systemic steroids (prednisone or equivalent), and immunomodulators) compared with those who were intolerant to or had an inadequate response to approved biologic therapies (infliximab, adalimumab, certolizumab pegol, natalizumab, vedolizumab and/or ustekinumab)[100]. Risankizumab was also significantly more effective than placebo in inducing and maintaining endoscopic outcomes in the overall patient population. Specifically, patients receiving 600 mg intravenous risankizumab every 4 weeks in the ADVANCE and MOTIVATE trials ($n = 527$) had higher rates of endoscopic response (36.1% versus 11.6%), endoscopic remission (22.4% versus 6.6%), and ulcer-free endoscopy (SES-CD ulcerated surface subscore of 0 in patients with SES-CD ulcerated surface subscore ≥1 at baseline; 18.5% versus 5.8%) compared with placebo ($n = 362$) at week 12 ($P < 0.001$ for all comparisons)[100]. Similar trends were observed in a subanalysis of the FORTIFY maintenance trial: patients receiving 360 mg subcutaneous risankizumab ($n = 141$) every 8 weeks had higher rates of endoscopic response (46.5% versus 22.0%), endoscopic remission (39.1% versus 12.8%), ulcer-free endoscopy (30.5% versus 10.5%), and deep remission

(29.1% versus 10.4%) compared with placebo (n = 164) at week 52 (P < 0.001 for all comparisons)[100].

In subgroup analyses of the phase III trials examining the relationship between disease location and response to risankizumab treatment, patients with colonic and ileal colonic Crohn's disease treated with risankizumab achieved significantly higher rates of the co-primary and composite endpoints of clinical remission and endoscopic response, and endoscopic remission at weeks 12 and 52, as well as sustained (week 12 and week 52) endoscopic remission at week 52 compared with patients treated with placebo disease[101]. Patients with ileal disease had lower rates relative to patients with colonic and ileal colonic disease for nearly all outcomes assessed at both weeks 12 and 52, although analyses at the latter timepoint were limited by a small number of patients with ileal disease (n = 15).

Guselkumab.—In the phase II GALAXI 1 trial, patients were randomly assigned to either intravenous treatment with 200 mg (n = 61), 600 mg (n = 63) or 1,200 mg (n = 61) guselkumab at weeks 0, 4 and 8; 6 mg kg^{-1} intravenous ustekinumab at week 0 and 90 mg subcutaneous ustekinumab at week 8 (n = 63); or intravenous placebo (n = 61). At week 12, significantly greater reductions from baseline CDAI (the primary endpoint) were reported in all guselkumab dose groups compared with the placebo group (Supplementary Table 1). Significant differences at week 12 were also observed for all guselkumab dose groups for the outcomes of clinical response, clinical remission, Patient-Reported Outcome-2 (PRO-2) remission, clinical biomarker response and endoscopic response[102,103]. In a treat-straight-through maintenance study design, patients randomized during induction to guselkumab 200 mg intravenously received 100 mg subcutaneously every 8 weeks, while those who received induction with either 600 mg or 1,200 mg intravenously received 200 mg subcutaneously every 4 weeks. Rates of CDAI clinical remission at week 48 ranged from 57.4% to 73.0%[104].

Brazikumab.—Patients were randomized to treatment with 700 mg intravenous brazikumab (n = 59) or placebo (n = 60) at weeks 0 and 4, followed by open-label 210-mg subcutaneous brazikumab (n = 52) every 4 weeks from week 12 onwards in a phase IIa study. The primary end point, which was clinical response at week 8, was achieved in 49.2% of patients treated with brazikumab compared with 26.7% of patients treated with placebo (absolute difference 22.5%; 95% CI 5.6–39.5%, P = 0.010)[105].

Mirikizumab.—Patients in the phase II SERENITY trial were randomized to treatment with 200 mg (n = 31), 600 mg (n = 32) or 1,000 mg (n = 64) intravenous mirikizumab, or placebo (n = 64), at weeks 0, 4 and 8. At week 12, rates of endoscopic response were significantly greater in the 600-mg and 1,000-mg mirikizumab groups compared with placebo[106] (Supplementary Table 1). Patients who received mirikizumab and achieved ≥1 point improvement in SES-CD score at week 12 were re-randomized to either continue their intravenous treatment assignment (IV-C) or to 300 mg mirikizumab subcutaneously every 4 weeks. Endoscopic response rates at week 52 were 58.5% and 58.7% in the IV-C and subcutaneous groups, respectively. Furthermore, of those with endoscopic response at week 12, 69.6% and 66.7% in the IV-C and subcutaneous groups, respectively, achieved endoscopic response at week 52 (ref. 107).

Briakinumab.—In a phase IIb study, patients were randomized to treatment with 400 mg (n = 45) or 700 mg (n = 139) intravenous briakinumab or placebo (n = 46) at 0, 4 and 8 weeks (Supplementary Table 1). At week 6, there was no significant difference in the proportion of patients achieving clinical remission in either the 400-mg or 700-mg briakinumab treatment groups compared with the placebo group. This trial was terminated by the sponsor owing to lack of efficacy[108].

A discussion on potential future positioning and use of these agents in particular patient populations based on current available data appears later.

Moderate-to-severe ulcerative colitis

Ustekinumab.—In the phase III UNIFI trial, patients were randomized to receive induction treatment with 130 mg (n = 320) or ~6 mg kg^{-1} (n = 322) intravenous ustekinumab (n = 322) or placebo[109]. At week 8, the proportion of patients who achieved clinical remission (total score of ≤2 on the Mayo Score and no subscore >1 on any of the four Mayo Score components) was significantly greater in the 130 mg and ~6 mg kg^{-1} ustekinumab groups compared with placebo (Supplementary Table 2). At week 8, clinical responders to ustekinumab were re-randomized to receive 90 mg subcutaneous ustekinumab every 8 or 12 weeks or placebo. The proportion of patients receiving ustekinumab every 8 or 12 weeks in clinical remission at week 44 was significantly greater compared with placebo[109]. Endoscopic and histological outcomes analysed in the UNIFI trial also significantly favoured ustekinumab treatment over placebo during both the induction and maintenance phases of the trial and are described in detail in Supplementary Table 2. In long-term follow-up of patients who were week 8 or 16 responders (n = 428) and received ustekinumab maintenance therapy, those who achieved histo-endoscopic mucosal healing (Mayo Endoscopic Subscore ≤1 and neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue based on the Geboes Score; n = 116 (26.5%)) after induction had higher rates of long-term (weeks 92 and 152) symptomatic and corticosteroid-free symptomatic remission than those who had endoscopic (n = 30 (6.8%)) or histological (n = 106 (24.2%)) improvement alone after induction. Although rates of both remission outcomes decreased between weeks 92 and 152 in patients who achieved either endoscopic or histological improvement alone, patients with histo-endoscopic mucosal healing maintained symptomatic remission over the same time period[110].

Mirikizumab.—The phase III LUCENT-1 trial evaluated the efficacy of mirikizumab induction therapy (300 mg intravenously every 4 weeks, n = 868) compared with placebo (n = 294). At week 12, the mirikizumab group had significantly higher clinical remission rates compared with the placebo group (24.4% versus 13.3%, P = 0.00006). Endoscopic remission and histologic-endoscopic mucosal improvement rates were also significantly higher at week 12 in the mirikizumab group than in the placebo group[111] (Supplementary Table 2).

Guselkumab.—In the phase IIb QUASAR study, patients were randomized to treatment with 200 mg (n = 101) or 400 mg (n = 107) intravenous guselkumab or placebo (n = 105) at weeks 0, 4 and 8. The primary outcome, which was clinical response at week 12,

was achieved by 61.4% and 60.7% of patients in the guselkumab 200 mg and 400 mg groups, respectively, compared with 27.6% of those in the placebo group ($P < 0.001$ for both comparisons to placebo). Significantly higher rates of endoscopic improvement, histo-endoscopic mucosal improvement, and endoscopic normalization were also achieved in both guselkumab dose groups compared with placebo at week 12 (ref. 112) (Supplementary Table 2).

Given the favourable safety profile of the IL-12 and IL-23 agents (see next section), combining anti-IL-12 or anti-IL-23 agents with one or more biological agents and/or small molecules might be possible. The phase II VEGA study was the first trial to combine two biologics for the treatment of IBD, comparing the efficacy of guselkumab and golimumab combination therapy with monotherapy with either agent[113] (Supplementary Table 2). Patients were randomized to golimumab 200 mg subcutaneously at week 0, 100 mg subcutaneously at week 2 and then every 4 weeks ($n = 72$); guselkumab 200 mg intravenously at weeks 0, 4 and 8 ($n = 71$); or the combination of golimumab and guselkumab at the same doses as in the monotherapy arms ($n = 71$), and followed to week 12. All patients were naive to TNF inhibitors as well as to ustekinumab and anti-IL-23 antibodies. The primary endpoint, which was clinical response at week 12, was achieved by 61.1% of patients in the golimumab monotherapy group and 74.6% of patients in the guselkumab monotherapy group compared with 83.1% in the combination group ($P = 0.003$ compared with golimumab alone and $P = 0.215$ compared with guselkumab alone). The proportions of patients with endoscopic improvement, endoscopic normalization, histological remission, both histological remission and endoscopic improvement, and both histological remission and endoscopic normalization were higher in the combination group compared with either the guselkumab or golimumab monotherapy groups (Supplementary Table 2).

A discussion on potential future positioning and use of these agents in particular patient populations based on currently available data appears later.

Safety of targeting IL-12 and IL-23

Most adverse effects reported in randomized controlled trials (RCTs) of agents targeting IL-12/IL-23 were mild, non-serious and did not require treatment discontinuation. Serious adverse effects, infections (including serious infections) and malignancies reported in phase II and III RCTs and open-label extensions of these trials in Crohn’s disease and ulcerative colitis (ustekinumab only) are shown in Table 2 and do not appear to differ compared with placebo treatment.

As the first agent in this class approved for the treatment of various autoimmune disorders, including IBD, the most safety data available are for ustekinumab. In a pooled safety analysis of results from phase II and phase III studies (1,733 patient-years of follow-up), the number of patients with serious adverse events (27.50 (95% CI 23.45–32.04) versus 21.23 (95% CI 19.12–23.51)), infections (80.31 (95% CI 73.28–87.84) versus 64.32 (95% CI 60.60–68.21)), serious infections (5.53 (95% CI 3.81–7.77) versus 5.02 (95% CI 4.02–6.19)), and malignancies excluding nonmelanoma skin cancer (0.17 (95% CI 0.00–0.93)

versus 0.40 (95% CI 0.16–0.83)) were similar between placebo and ustekinumab[114]. These results are further supported by data from the Psoriasis Longitudinal Assessment and Registry (PSOLAR) showing no increased risk for serious infections or malignancy with 12,472 patient-years of follow-up for ustekinumab[115], as well as by data from observational 'real world' ustekinumab studies[116]. In their systematic review and meta-analysis, Honap and colleagues[116] found a total of 498 adverse events reported in 2,977 patients (16.7%) for a pooled estimate of incidence rate of 13.5 (95% CI 9.6–18.6). Rates of serious infection (69 out of 1,749; 3.9%) and serious adverse events (86 out of 1,534; 5.6%) were low and comparable to those reported in the IM-UNITI RCT (5.6% versus 9.9–12.1% and 3.9% versus 2.3–5.3% real-world versus trials, respectively).

The phenotypes of patients with various genetic mutations or defects in the IL-12 and IL-23 pathway might also provide insights into hypothetical safety consequences associated with targeting this pathway. As previously discussed, *IL23R*^{R381Q} carriers do not seem to be more vulnerable to infection generally; however, individuals with rare, significant loss-of-function mutations in other genetic components of the IL-23–T_H17 pathway, including those common to IL-12 and IL-23 such as p40 and IL12βR1, demonstrate increased susceptibility to some infections (such as *Salmonella*, *Candida* and tuberculosis)[117,118]. As also previously noted, experimental animal models have demonstrated that IL-23 is required for regulation of responses to resident (for example, segmented filamentous bacteria) and pathogenic (for example, *Listeria monocytogenes*) bacteria[119–123]. Importantly, IL-23 compensates for IL-12 deficiency in both mice and humans during infectious challenge (for example, *Mycobacterium* and *Salmonella* Enteritidis)[117,124]. Despite these findings, as supported by the evidence described previously, increased susceptibility to infection has not yet been observed in patients with IBD treated with IL-12 and IL-23 neutralizing antibodies.

Although long-term safety data for many compounds are still accumulating, the available evidence from RCTs and real-world data suggests that neutralizing IL-12 and/or IL-23 is a safe strategy for the treatment of IBD.

IL-12 and IL-23 therapies: precision medicine

Molecular predictors

Biomarkers that predict response before treatment might identify patients who are more likely to benefit and reduce time associated with cycling through ineffective therapeutic interventions. Patients with Crohn's disease who are unresponsive to TNF inhibitors had a significant upregulation of genes associated with IL-23R-dependent pathways compared with responders[125]. Furthermore, upregulation of IL-23p19, IL-23R, IL-17A and associated downstream phosphorylated STAT3 was observed in patients with non-response compared with responders. These results suggest that patients with non-response to TNF inhibitors might be good candidates for IL-23-targeted therapy[125], although this is not always supported by clinical evidence[98,107,126].

Few studies have investigated biomarkers predictive of response to IL-12 and/or IL-23 inhibition. A higher pre-treatment serum concentration of IL-22 was associated with a higher likelihood of response to brazikumab treatment in patients with Crohn's disease[105].

However, pre-treatment expression levels of IL-22-responsive gene transcripts in colonic biopsy samples from patients with Crohn's disease was not predictive of response to ustekinumab[57]. The association between baseline faecal microbiota composition and diversity and therapeutic response to ustekinumab in the CERTIFI study has also been analysed[127]. Patients with Crohn's disease in remission were distinguishable from those with active disease 6 weeks after treatment according to baseline microbiota composition and clinical data (area under the curve 0.844; specificity 0.831, sensitivity 0.774). The median baseline community diversity in patients in remission was 1.7 times higher than in patients with active disease after treatment. Microbiota diversity increased over the 22 weeks of the study, in parallel with disease improvement, in patients with a response to ustekinumab, but not in those who were unresponsive to treatment. These baseline differences and changes in faecal microbiota in response to therapy suggest the potential for a noninvasive biomarker to initiate or monitor ustekinumab treatment. Validation in an external cohort and demonstration of an ustekinumab-specific signature is necessary given that the observations might simply reflect a milder disease phenotype and a higher probability of response.

Despite the lack of strong evidence for predictive biomarkers, IL-17 and IL-22 (cytokines downstream of IL-23) have been identified as pharmacodynamic biomarkers of IL-23 inhibition in RCTs. Patients with ulcerative colitis treated with mirikizumab had a reduction in IL-22 and IL-17 plasma concentrations from baseline to week 12 in a phase II RCT[128]. Similarly, *IL22* gene expression was significantly reduced from baseline to week 12 in ileal biopsy samples from patients with Crohn's disease treated with risankizumab compared with placebo[129].

Clinical predictors

Few studies have identified clinical or demographic parameters associated with response to ustekinumab (reviewed elsewhere[130]). Post-hoc analyses for baseline clinical predictors of response to IL-12 and/or IL-23 inhibition have been conducted for several RCTs targeting IL-23 (discussed previously), but no significant findings have been reported. Indeed, inconsistent patterns of response to mirikizumab or risankizumab based on previous biologic exposure have been reported[98,107,126]. As it relates to predictors of treatment failure, bowel frequency and >2 previous biologic exposures were positively associated with time to ustekinumab dose intensification from every 8 weeks to every 4 or 6 weeks in a retrospective cohort study of 108 patients with ulcerative colitis[131]. Perianal disease, higher Harvey–Bradshaw Index scores, and opioid use were identified as predictors of failure to achieve remission in response to ustekinumab dose intensification in a retrospective cohort study of 123 patients with Crohn's disease[132].

Pharmacological predictors.—Differences in sex, body weight, serum albumin concentration or inflammatory burden can partially explain the inter-individual and intra-individual variability in drug clearance that is observed with intravenously or subcutaneously administered biologics targeting IL-12 and/or IL-23 (refs. 133,134). Immunogenicity has not been identified as a pharmacologically or clinically relevant factor given the low rates observed to date[135], and therefore the use of concomitant immunomodulators to

influence drug exposure or treatment outcomes might not be an important consideration for biologics that target IL12 and/or IL-23, unlike for those that target TNF[136]. Evaluation of the relationship between drug concentrations and outcomes has therefore emerged as a primary focus. An exposure–response relationship has been observed for ustekinumab[137–139] but has not yet been demonstrated in a prospective interventional study. Previous studies in patients with Crohn's disease treated with ustekinumab[137,138] showed that higher serum ustekinumab concentrations during induction treatment were associated with clinical, endoscopic and biomarker (CRP and faecal calprotectin)-based outcomes at the end of induction and during maintenance therapy. Similar results were observed for patients with ulcerative colitis, including an association between ustekinumab[139] serum concentrations and histological improvement. An association between serum risankizumab concentrations and CDAI response and remission, as well as endoscopic response, was observed in patients with Crohn's disease[129]. However, no difference in serum mirikizumab concentrations was observed between responders and non-responders during induction and maintenance therapy[107]. To mitigate the effect of patient demographics and disease characteristics on mirikizumab drug clearance and exposure, Sandborn and colleagues[128] employed a unique approach that adjusted induction dosing based on actual serum concentrations. Serum mirikizumab concentrations were therefore similar in patients who required dose adjustments to those who did not in both the 50-mg and the 200-mg groups, and the clinical response and remission rates were similar[128]. Future interventional studies are required to confirm drug exposure levels to optimize efficacy across the patient population for all biologic therapies[140].

Positioning anti-IL-12/IL-23 agents in IBD

The anti-IL-12/IL-23p40 agent ustekinumab is the only drug in this class currently approved for the treatment of both Crohn's disease and ulcerative colitis, and risankizumab, an anti-IL-23p19 agent, has also been approved for the treatment of Crohn's disease. Other anti-IL-23p19 agents (brazikumab, mirikizumab and guselkumab) are in late-stage development and are expected to be commercially available in the foreseeable future[141–143]. Positioning these agents in treatment algorithms and/or appropriate patient selection will be critical. Risankizumab demonstrated superior efficacy to ustekinumab for the treatment of psoriasis[144], and a similar phase III trial comparing both drugs in patients with Crohn's disease with previous TNF inhibitor treatment is currently ongoing (NCT04524611).

Data from head-to-head trials might provide information not only on appropriate patients for specific compounds on a population level, but also shed light on positioning among the various classes. However, similar clinical and endoscopic remission rates were observed in the SEAVUE trial, which compared ustekinumab with adalimumab monotherapy in biologic-naive patients with Crohn's disease, with higher infection rates observed in the adalimumab group[145].

The current paucity of head-to-head trials and lack of robust molecular markers requires reliance on indirect comparisons. Network meta-analyses have investigated the efficacy and safety of biologics and small molecules in moderate-to-severe Crohn's disease and ulcerative colitis. For patients with Crohn's disease who failed treatment with

TNF inhibitors, Singh and colleagues proposed IL-23-targeted therapy (ustekinumab and risankizumab) as the proposed mechanism of action, with risankizumab demonstrating superiority over the anti-α4β7 integrin antibody vedolizumab for induction of clinical remission[146]. In patients refractory to TNF inhibitors, IL-23 has a marked effect on shaping the immune landscape of the inflamed intestine. Specifically, IL-23 controls expansion of apoptosis-resistant intestinal $TNFR2^{+}IL\text{-}23R^{+}$ T cells, leading to molecular resistance to TNF inhibitor therapy in Crohn's disease. These findings identify IL-23 as a suitable molecular target in patients with IBD refractory to TNF inhibitor therapy[125].

The highest rates of clinical remission and endoscopic improvement in patients with ulcerative colitis previously treated with TNF inhibitors were observed with ustekinumab and tofacitinib, as reported by Singh and colleagues[147]. A separate network meta-analysis ranked ustekinumab highest among biologics for achieving the outcomes of clinical response and remission and endoscopic response in the same patient population[148]. The lowest total number of adverse events was observed for ustekinumab. In another study, ustekinumab was ranked highest for the outcome of endoscopic improvement in a network meta-analysis of outcomes in patients with ulcerative colitis naive to biologic therapy, was significantly superior to adalimumab and vedolizumab, and ranked second (after tofacitinib) for induction of endoscopic improvement in patients with previous exposure to biologic therapy[149]. Although translation of these data into clinical practice would ideally be further supported by validation in head-to-head clinical trials, these data provide relevant interim information to help guide clinical decision-making.

Ustekinumab was effective for treatment of extraintestinal manifestations, particularly arthralgia, psoriatic arthritis, psoriasis, pyoderma gangrenosum, and erythema nodosum in a systematic review and meta-analysis encompassing 254 patients with IBD and extraintestinal manifestations. No efficacy was observed in axial spondyloarthritis[150]. These agents might thus represent an important and safe alternative to TNF inhibitors, which are the primary therapeutic option for this indication. Indeed, TNF inhibitors can paradoxically induce or worsen psoriatic skin lesions in 1.6–2.7% of patients with IBD, with infliximab most frequently associated with these reactions (52.6–62.5% of reported cases)[151]. Switching to anti-IL-12/IL-23 agents has been reported as effective (and should be considered) when withdrawal of TNF inhibitors is warranted due to lesion severity or insufficient response to topical treatment[151,152].

Other patients who might benefit from anti-IL-12/IL-23 treatments are those for whom safety is a primary consideration, including older people and those with malignancy or infection. Although favourable safety outcomes were observed in the ustekinumab UNITI and IM-UNITI trials (including up to 5 years of follow-up data in the long-term extension of IM-UNITI)[153], the average age of participants was 38 and age stratification was not performed[93]. However, no significant differences in infection rates (5.2% versus 7.7%, $P = 0.7$), infusion reactions (2.6% versus 6.4%, $P = 0.77$) or postsurgical complications ($P = 0.99$) by age category were observed in a retrospective study comparing ustekinumab in patients with Crohn's disease aged ≥65 years ($n = 39$) to those <65 years ($n = 78$)[154]. Similarly, safety data from patients with psoriasis ≥65 years of age reported no concerning safety signals, further supporting the potential for ustekinumab in this population[155].

Future evidence-based recommendations for positioning of anti-IL-12/IL-23 therapies for the treatment of patients with IBD should be based on additional RCT data, including data from trials that directly compare the efficacy and safety of these agents with other classes of therapies.

Conclusions

A wealth of experimental data from in vitro, animal model and human genetic association studies support a pivotal role for IL-23 in the pathogenesis of IBD and other immune-mediated diseases. These data are supported clinically by the efficacy observed in pivotal controlled trials of agents targeting IL-23 (and in some cases IL-12) for the treatment of Crohn's disease and ulcerative colitis, and which has led to the approval of ustekinumab for the treatment of both forms of IBD. There is evidence (discussed previously) suggesting that targeting IL-23 clinically might have deleterious effects on the maintenance of intestinal epithelial barrier integrity and/or microbial clearance, but infection rates, including rates of serious infections, do not seem to be increased with treatments targeting IL-23, although most long-term and real-world data supporting this observation have been accumulated for ustekinumab. To conclude that these observations are generalizable to the therapeutic class, longer-term data are needed for other agents under investigation. Nevertheless, the safety profile of these agents is encouraging: ustekinumab is approved as the first-line treatment for moderately-to-severely active Crohn's disease and ulcerative colitis, and risankizumab was most recently approved by the FDA in June 2022 for the treatment of moderately-to-severely active Crohn's disease. Again, whether this positioning will be consistent across all investigational agents in this class depends on the results of ongoing controlled trials. Precision medicine research should aim to provide a deeper understanding of the mechanism of action of these agents and to better define potential complementary and/or synergistic effects with other biologic or small-molecule therapies. This knowledge will further facilitate the appropriate positioning of these therapies and guide therapeutic decision-making based on the molecular backgrounds of individual patients. Late-phase clinical trial data also support the potential use of these therapies in specific patient populations, including older people, and those with previous malignancy, higher infection risk or psoriasis (including those with TNF inhibitor-mediated onset). Head-to-head studies and clinical tools that integrate potential clinical and biological predictors of response to various therapeutic agents will further enable personalized medicine-based treatment decisions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

- IL-12 and IL-23, which are members of the IL-12 family of cytokines, have a key role in intestinal homeostasis and inflammation, including in inflammatory bowel disease.
- Multiple IL-12- and/or IL-23-neutralizing antibodies have been tested in immune-mediated diseases, including Crohn's disease and ulcerative colitis.
- In addition to demonstrated efficacy for clinical, endoscopic and histological outcomes, targeting IL-12 and/or IL-23 is a safe treatment strategy.
- The exact positioning of such antibodies in current treatment algorithms will be influenced by ongoing head-to-head trials and evaluation of predictive molecular markers.

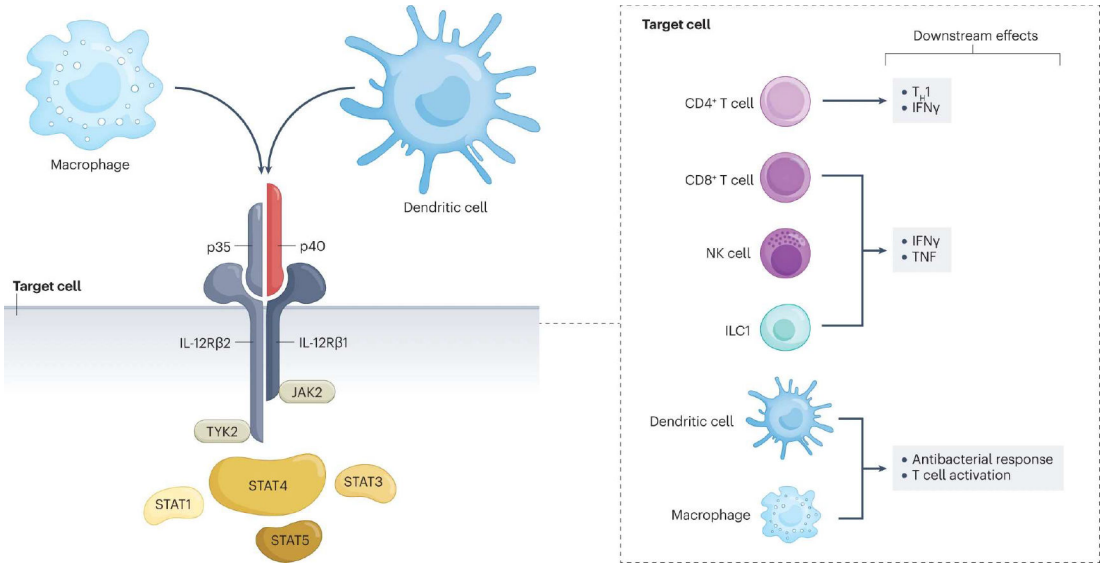

Fig. 1 |. Cellular sources, target cells, signalling and downstream effects of IL-12.

Interleukin-12 (IL-12) is a heterodimeric cytokine comprised of p40 (also part of the IL-23 dimer) and p35 subunits. It is produced by macrophages and dendritic cells. The receptor for IL-12 is composed of two different subunits, IL-12Rβ1 and IL-12Rβ2, which undergo conformational changes upon binding to IL-12 and bring into proximity two cytoplasmic tyrosine kinases, the Janus kinase 2 (JAK2) and tyrosine kinase 2 (TYK2), which are essential for downstream signalling of IL-12. JAKs trans/autophosphorylate each other and the receptor. Receptor phosphorylation enables binding and phosphorylation of signal transducers and activators of transcription (STATs), mainly STAT4. Phosphorylated STATs dimerize and translocate to the nucleus, where they regulate gene transcription. Different cell types express the IL-12 receptor on their membrane and are therefore targets for IL-12. Depending on the cell target, IL-12 exerts a variety of downstream effects. In naive $CD4^+$ T cells, STAT4 signalling together with T-bet induce differentiation towards the T helper 1 (T_H1) cell phenotype and production of interferon-γ (IFNγ). In $CD8^+$ T cells, natural killer (NK) cells and group 1 innate lymphoid cells (ILC1s), IL-12 induces IFNγ and tumour necrosis factor (TNF) release. Finally, IL-12 signalling on dendritic cells and macrophages amplifies the antibacterial response and T cell activation.

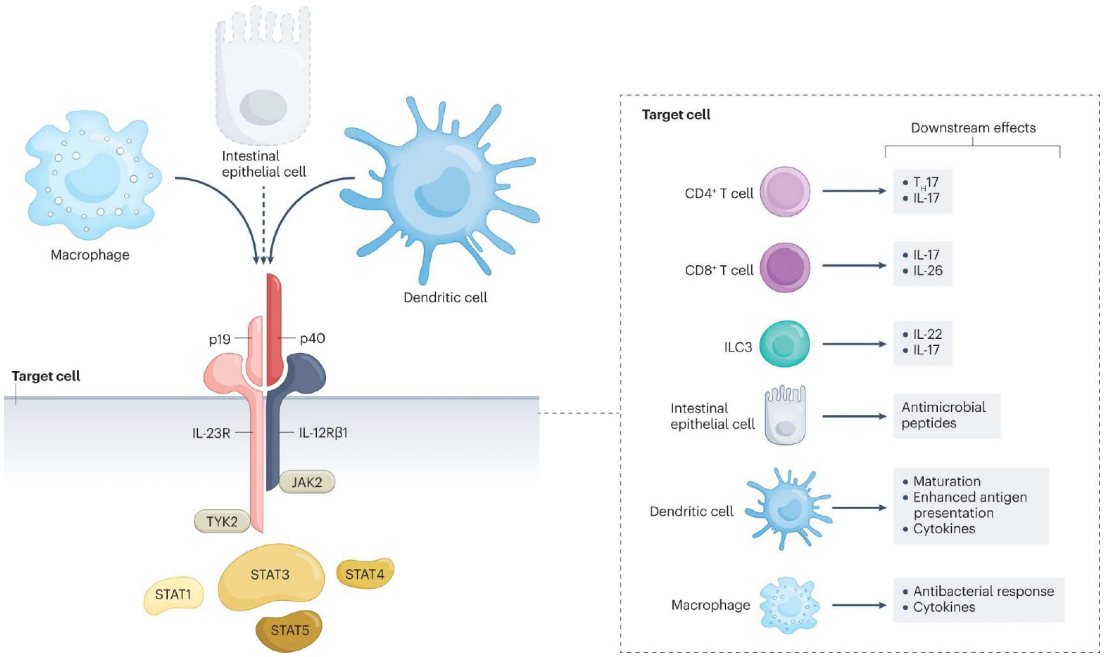

Fig. 2 |. Cellular sources, target cells, signalling and downstream effects of IL-23.

Interleukin-23 (IL-23) is a heterodimeric cytokine composed of p40 (also part of the IL-12 dimer) and p19 subunits. Like IL-12, and in response to similar stimuli (microbial signals, cytokines and co-stimulatory T cell ligands), IL-23 is produced by macrophages and dendritic cells. Some publications[5–7] also show production of IL-23 by intestinal epithelial cells (dashed line, will need further confirmatory evidence). The IL-23 receptor is comprised of the IL-12Rβ1 and the IL-23R chains. Binding of IL-23 induces a conformational change that brings two cytoplasmic tyrosine kinases, Janus kinase 2 (JAK2) and tyrosine kinase 2 (TYK2), into proximity. JAKs trans/autophosphorylate each other and the receptor. Receptor phosphorylation enables binding and phosphorylation of signal transducers and activators of transcription (STATs), predominantly the STAT3 transcription factor. Phosphorylated STATs dimerize and translocate to the nucleus, where they regulate gene transcription. The IL-23 receptor is expressed on numerous cell types, including lymphoid cells, specifically $CD4^+$ T helper 17 (T_H17) and $CD8^+$ T cells[8]. Innate lymphoid cells (ILCs), such as ILC3, also express the receptor and readily produce IL-22 and IL-17 cytokines in response to IL-23 stimulation. In IECs, IL-23 induces the expression of antimicrobial peptides. Furthermore, dendritic cells and macrophages respond to IL-23 stimulation by secreting a variety of cytokines. In addition, when the IL-23 receptor is engaged, dendritic cells demonstrate enhanced maturation and antigen presentation, and macrophages show an increased antibacterial response.

Table 1 |

Role of IL-23 in mucosal homeostasis and disease

Cell type	Pathway and/ or signalling molecules	Effect
Innate immune system		
Type 3 innate lymphoid cell	IL-23R/STAT5	Cell activation Cytokine production (IL-17A, IL-22) Antimicrobial effects
Granulocyte	IL-23R	Cell activation Pro-inflammatory cytokine production
Natural killer/intraepithelial lymphocytes	IL-23R	Cytotoxicity Cell activation Pro-inflammatory cytokine production
Adaptive immune system		
T_{reg} Cells, T_{eff} cells, T_H17 cells	IL-23R RORγt (T_{eff} cells)	Suppression of T_{reg} cells Proliferation and expansion of T_H17 cells Production of IL-6 and T_H17 cytokines
Intestinal epithelial cells	IL-22 Regenerating gene family proteins	Increased barrier function Antimicrobial effects

Interleukin-23 (IL-23) exerts effects on both innate and adaptive immune cells. In type 3 innate lymphoid cells, granulocytes, intraepithelial lymphocytes and natural killer cells, IL-23 induces cell activation and cytokine production. Additional effects of IL-23 are related to adaptive immune cells, such as regulatory T (T_{reg}) cells, and effector T (T_{eff}) cells, such as T helper 17 (T_H17) cells. In this context, IL-23 suppresses T_{reg} cells, whereas it activates T_H17 cells. Furthermore, this cytokine regulates barrier function and production of antimicrobial peptides in intestinal epithelial cells. IL-23R, IL-23 receptor; RORγt, retinoid-related orphan receptor-γt; STAT, signal transducer and activator of transcription.

Table 2 |

Serious adverse events, infections and malignancies reported in maintenance and/or open-label extension trials

Agent	Serious adverse events	Infections	Malignancies
Ustekinumab			
UNITI-IM[93] (phase III CD)	Placebo: 20/133 (15%) 90mg every 12weeks: 16/106 (12.1%) 90mg every 8weeks: 13/131 (9.9%)	Any Placebo: 66/133 (49.6%) 90mg every 12weeks: 61/106 (46.2%) 90mg every 8weeks: 63/131 (48.1%) Serious Placebo: 3/111 (2.3%) 90mg every 12weeks: 7/106 (5.3%) 90mg every 8weeks: 3/131 (2.3%)	Basal cell carcinoma Placebo: 1 90mg every 8weeks: 1
UNIFI[109] (phase III UC)	Placebo: 17/175 (9.7%) 90mg every 12weeks: 13/172 (7.6%) 90mg every 8weeks: 15/176 (8.5%)	Any Placebo: 81/175 (46.3%) 90mg every 12weeks: 58/172 (33.7%) 90mg every 8weeks: 86/176 (48.9%) Serious Placebo: 4/175 (2.3%) 90mg every 12weeks: 6/172 (3.5%) 90mg every 8weeks: 3/176 (1.7%)	Excluding non-melanoma skin cancer Placebo: 0 90mg every 12 weeks: 1/172 (0.6%) 90mg every 8 weeks: 1/176 (0.6%)
SEAVUE[96] (phase III CD)[a]	Adallmumab: 32/195 (16.4%) Ustekinumab: 25/191 (13.1%)	Any Adallmumab: 79/195 (40.5%) Ustekinumab: 65/191 (34.0%) Serious Adalimumab: 5/195 (2.6%) Ustekinumab: 4/191 (2.1%)	Adalimumab: 1/195 (0.5%, basal cell carcinoma) Ustekinumab: 0
Risankizumab			
M15–993 (ref. 129) (phase II CD)[b]	Period 2: 18 (62.5) Period 3: 9 (20.8) Periods 1–3: 46 (42.2)	Any Period 2: 37 (128.5) Period 3: 32 (73.9) Periods 1–3: 107 (98.1) Serious Period 2: 1 (3.5) Period 3: 1 (2.3) Periods 1–3: 5 (4.6)	None
M15–989 (ref. 156) and M16–000 (ref. 156) (phase II and III open-label extension CD)[c]	23 (35.4%); 24.6	Any 48 (73.8%); 112 Serious 6 (9.2%); 4.2	None
FORTIFY[99] (phase III CD)[d]	360mg: 21.0 180mg: 19.5 Placebo: 19.3	Serious 360mg: 6.0 180mg: 3.0 Placebo: 5.0	Not reported
Guselkumab			
GALAXI[104] (phase II CD)[e]	≥1 serious adverse events 200mg IV followed by 100mg SC: 6 (8.2%) 600 mg IV followed by 200 mg SC: 5 (6.8%) 1,200mg IV followed by 200mg SC: 5 (6.8%)	≥1 infection 200 mg IV followed by 100 mg SC: 25 (34.2%) 600mg IV followed by 200mg SC: 30 (41.1%) 1,200mg IV followed by 200 mg SC: 25 (34.2%) ≥1serious infection 200mg IV followed by 100mg SC: 2 (2.7%) 600mg IV followed by 200mg SC: 2 (2.7%) 1,200mg IV followed by 200mg SC: 1 (1.4%)	Not reported

CD, Crohn's disease; IV, intravenous; SC, subcutaneous; UC, ulcerative colitis.

[a] Adalimumab and ustekinumab administered at approved doses.

[b] Period 2 (week 26, *n*=101); period 3 (week 52, *n* = 62); periods 1–3 (weeks 12–52, *n*=115); data expressed as number of events per 100 patient-years.

[c] 184weeks (*n* = 65, 167 patient-years); data expressed as number of patients (%); events per 100 patient-years.

[d] 52 weeks; data expressed as exposure adjusted event rates per 100 patient-years.

[e] 48 weeks.