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Review Article

IL-12/IL-23 inhibitors: a promising approach to the treatment of inflammatory disorders

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CONTENTS

Abstract

Recent clinical trials with anti-interleukin (IL)-12p40 antibodies in psoriasis and Crohn's disease patients have demonstrated the therapeutic efficacy of this approach and have validated IL-12/IL-23 as an attractive target for the development of effective new drugs for the treatment of autoimmune and inflammatory disorders. IL-23, a new member of the IL-12 family, shares the p40 subunit with IL-12, and is similarly inhibited by anti-IL-12p40 antibodies. Emerging data clearly indicate that IL-23 is essential for the expansion and survival of Th17 T-cells, which have been identified as responsible for many of the inflammatory autoimmune responses. Investigation of the regulation of the p40 and the IL-23-specific p19 subunits led to the finding of a selective and dominant role for c-Rel in activating their promoters. This review describes drugs reported to inhibit the production of IL-12/IL-23, recent studies on their mechanisms of action in modulating the expression of these cytokines, and their potency and selectivity.

Introduction

Interleukin-12 (IL-12) is a heterodimeric cytokine (p70) comprised of two independently regulated protein subunits, p35 and p40. The well-documented biological functions of IL-12 are the induction of interferon gamma (IFN-γ) expression from T-cells and natural killer (NK) cells, and the differentiation of naïve T-cells to a Th1 cell type (1). In addition, the p40 subunit of IL-12 can dimerize with a p19 subunit and form IL-23 —a more recently discovered member of the IL-12 family that also promotes a Th1 response but has distinct functions from IL-12. IL-23 is required for the generation of effector memory T-cells and IL-17-producing T-cells (Th17), which play a significant role in the inflammatory response (2, 3). IL-12 and IL-23 are produced from phagocytic cells and antigen-presenting cells (APCs), in particular macrophages and dendritic cells (DCs), upon stimulation with bacteria, bacterial products such as lipopolysaccharide (LPS) and intracellular parasites (4). Although the inflammatory effector function of Th1 and/or Th17 cells is essential for the clearance of intracellular pathogens, the excessive production of proinflammatory cytokines leads to serious tissue damage typical of organ-specific autoimmunity (5).

IL-12/IL-23 has been validated as an attractive clinical target in a number of studies. Experiments using mice lacking the gene encoding the p40 subunit shared by IL-12 and IL-23 or lacking the IL-23-specific subunit p19 have demonstrated the integral role of IL-12/IL-23 in the pathogenesis of autoimmune and inflammatory disorders (6-12). Moreover, monoclonal antibodies to the IL-12/IL-23 p40 subunit have been shown to be effective in human clinical trials in Crohn's disease and psoriasis patients (13, 14). Although antibodies against IL-12/IL-23 could provide significant medical benefit, a small-molecule IL-12/IL-23 inhibitor that could be administered orally would be highly desirable.

Biological function of IL-12 and IL-23

Prior to the recent discovery of IL-23, the p40 subunit had been considered to be specific to IL-12. The use of p40 knockout mice or neutralizing antibodies to p40 established that this subunit is essential for the development of T-cell-mediated diseases, such as experimental allergic encephalomyelitis (EAE), collagen-induced arthritis (CIA) and inflammatory bowel disease (IBD), leading to the hypothesis that IL-12 and IL-12-induced IFN-γ-producing Th1 cells are central regulators of inflammation (7, 12, 15). However, IL-23 has been found to play a more integral role in pathogenesis than IL-12, according to recent findings indicating that IL-23p19 knockout mice are resistant to the induction of disease in CIA (9), EAE (6) and IBD models (16, 17), while IL-12p35, IL-12Rβ2 and IFN-γ knockout mice developed EAE and CIA (18). Moreover,

antibodies specific for IL-23p19 ameliorated EAE (19), and adoptive transfer of myelin oligodendrocyte (MOG)-specific Th17 cells, but not Th1 cells, induced EAE in recipient mice (20). Direct intradermal administration of IL-23 in mouse skin induced epidermal hyperplasia and altered epidermal differentiation through the production of IL-22 and IL-17 from IL-23-driven Th17 cells (21, 22).

The introduction of the IL-23/Th17 axis to the autoimmune inflammation landscape facilitated studies to determine its role in human diseases. The importance of the IL-23/Th17 pathway is indicated by a marked increase in IL-23 synthesis in human psoriatic lesions (23), decreases in the expression of p19 and p40 mRNA in psoriasis patients responding to some immunomodulating treatments (24, 25), and impressive improvements produced by an anti-IL-12/IL-23p40 antibody in studies in psoriasis patients (13). Monocyte-derived DCs from multiple sclerosis patients secrete elevated levels of IL-23 with a coincident increase in IL-17 production by T-cells (26). IL-17-secreting lymphocytes were detected in the cerebrospinal fluid of multiple sclerosis patients (27). Increases in IL-23 and IL-12 production were observed in lamina propria mononuclear cells (LPMCs) from patients with Crohn's disease, but not ulcerative colitis, and declined dramatically after anti-IL-12/IL-23p40 antibody treatment, associated with decreases in anti-CD2/anti-CD28-stimulated IL-17 and IL-6 production (28). Moreover, the levels of IL-23 in sera and synovial fluid were higher in rheumatoid arthritis patients than in osteoarthritis patients or healthy controls (29). Recent genetic studies have also demonstrated the association of the IL-23/Th17 pathway with susceptibility to Crohn's disease, ulcerative colitis and psoriasis (30, 31). Together, emerging data clearly suggest that the IL-23/Th17 pathway drives many autoimmune and inflammatory disorders, and that the blockade of IL-23 —a critical upstream trigger— could be an effective therapeutic strategy.

Signal transduction

The p40 subunit, a common subunit of IL-12 and IL-23, can be secreted as a monomer or a homodimer, whereas the IL-12p35 and IL-23p19 subunits are secreted only when associated with p40. Upon cell activation, the transcription of *p40*, *p35* and *p19* genes is induced to produce the biologically active heterodimer. The regulation of p40 expression has been studied in great detail and this knowledge led to the understanding of the mechanism of action of several IL-12 production blockers. The p40 promoter contains binding sites for several transcription factors including nuclear factor-κB (NF-κB), interferon regulatory factor 1 (IRF-1) and Ets family members. Among them, NF-κB is the most popular target for effective blockade of the activation of the promoter. The NF-κB family includes p65, RelB, c-Rel, p50 and p52 proteins. Although p50/p65 is the most common form of NF-κB to activate the promoters of many genes, including those for tumor necrosis factor-α (TNF-α) and IL-6, the c-Rel-containing form is essential for activation of the *p40* gene in macrophages (32). IL-12 production by $CD8^+$ DCs is also c-Rel-dependent, primarily due to its activation of the *p35* promoter rather than the *p40* promoter (33). Moreover, a recent study of the *p19* gene promoter showed that c-Rel binds to the κB sites on this promoter and controls *p19* gene expression in DCs (34). Thus, c-Rel is a specific transcriptional regulator of both IL-12 and IL-23. Similar to other members of the NF-κB family, c-Rel is constitutively expressed and retained in the cytosol as inactive homo- or heterodimeric proteins in association with the inhibitory protein IκB. A variety of stimuli activate an IκB kinase (IKK) complex that phosphorylates the IκB proteins, leading to proteolytic degradation of IκB and activation of a c-Rel-containing dimer. The free dimer translocates to the nucleus and activates gene expression by binding to the κB site on the promoters.

It was demonstrated that calmodulin (CaM) binds to c-Rel and p65 after their release from IκB and is able to inhibit nuclear transport of c-Rel while allowing p65 to translocate to the nucleus (35). Hydrogen peroxide (H_2O_2) and nitric oxide (NO) increase cytoplasmic CaM, leading to selective sequestration of c-Rel in the cytosol and consequent reduction of IL-12 production (36-38), supporting the regulatory role of CaM in c-Rel activation.

The involvement of mitogen-activated protein kinases (MAPKs) in LPS-induced IL-12 production has been extensively studied using SB-203580-, SP-600125- and PD-98059, specific inhibitors of p38, JNK and extracellular signal-regulated kinase (ERK), respectively. However, the effects of these inhibitors on the production of IL-12 can be positive or negative, depending on stimuli, cell populations and levels of other cytokines, such as IFN-γ and IL-10. SB-203580 blocked the expression of CD40-induced IL-12p40 in human monocyte-derived DCs, LPS-induced IL-12p40 in murine macrophage J774 cells and phorbol 12-myristate-13-acetate (PMA)-treated human monocytic THP-1 cells (39-41). SB-203580 is reported to upregulate LPS-induced IL-12p40 at the protein (intracellular and secreted) and mRNA levels in peripheral blood mononuclear cells (PBMCs) and whole blood, which appears to be dependent on IFN-γ produced by nonadherent cells (42). IL-12 production by LPS plus IFN-γ was enhanced by SB-203580 in peritoneal exudate macrophages only at lower concentrations of IFN-γ (43). The contradictory effects on IL-12 production were also seen with SP-600125. SP-600125 dose-dependently enhanced both LPS-induced IL-12p40 production from THP-1 cells and p70 production from human monocytes (39), while it inhibited LPS-induced IL-12p40 production from the promonocytic THP-1/CD14 cell line, which constitutively expresses the LPS receptor CD14 on its cell surface (44). Blockade of p38 and JNK pathways thus does not appear to assure consistent inhibition of IL-12, and may instead enhance production. PD-98059 either had no effect or enhanced IL-12p40 and p70 expression in human macrophages and DCs (40, 45-47).

Cyclic AMP (cAMP) is another major regulator of IL-12 production, according to evidence indicating the suppression of IL-12 production by cAMP-inducing

agents. Prostaglandin E_2 (PGE_2), a well-known cAMP inducer, potently suppressed IL-12 production (48-50).

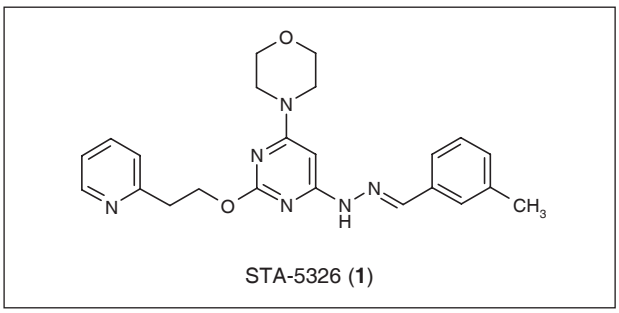
Anti-IL-12/IL-23 antibodies

CNTO-1275 (ustekinumab) and ABT-874 are human IgG_1 monoclonal antibodies specific for the p40 subunit that block the binding of both IL-12 and IL-23 to their receptors. Recent double-blind, placebo-controlled phase II trials of subcutaneous administration of both anti-p40 antibodies in psoriasis patients demonstrated clinical success comparable to blockade of TNF-α (13, 51), providing strong evidence for the important role of IL-12/IL-23 cytokines in the pathophysiology of psoriasis. The evaluation of mRNA expression in psoriatic skin lesions following CNTO-1275 treatment showed that the expression levels of type 1 cytokines (IFN-γ) and chemokines (IL-8, IFN-inducible protein 10 [IP-10] and monocyte chemotactic protein 1 [MCP-1]) were significantly reduced at 2 weeks post-treatment (52). A statistically significant reduction in infiltrating T-cells (17%) and a slight reduction in $CD11c^+$ DCs were seen in patients with a strong beneficial clinical response.

A monoclonal antibody to the IL-23-specific p19 subunit is also under preclinical development for multiple sclerosis. In EAE, early anti-IL-23p19 treatment reduced encephalitogenic T-cell and inflammatory myeloid cell invasion into the CNS, and treatment during the active disease phase prevented epitope spreading of $CD4^+$ T-cells and inhibited subsequent disease relapse (19).

Compounds under development that block IL-12 production through regulation of the NF-κB pathway (Fig. 1, Table I)

STA-5326 (**1**) is a small molecule that was developed from a novel triazine derivative identified through high-throughput IL-12 inhibitor screening (53). STA-5326 suppresses the synthesis of IL-12 and IL-23 in myeloid leukocytes through suppression of c-Rel nuclear accumulation. The inhibition is selective to c-Rel, as there is no effect on other members of the Rel/NF-κB family. In agreement with the mechanism of action, the compound selectively inhibits IL-12 and IL-23, with no significant suppression of other cytokines. Oral administration of STA-5326 led to a suppression of the Th1 but not the Th2 immune response in mice and markedly reduced inflammatory histopathological changes in an IBD model. In a biomarker study in which patients with stable psoriasis vulgaris skin plaques



STA-5326 (**1**)

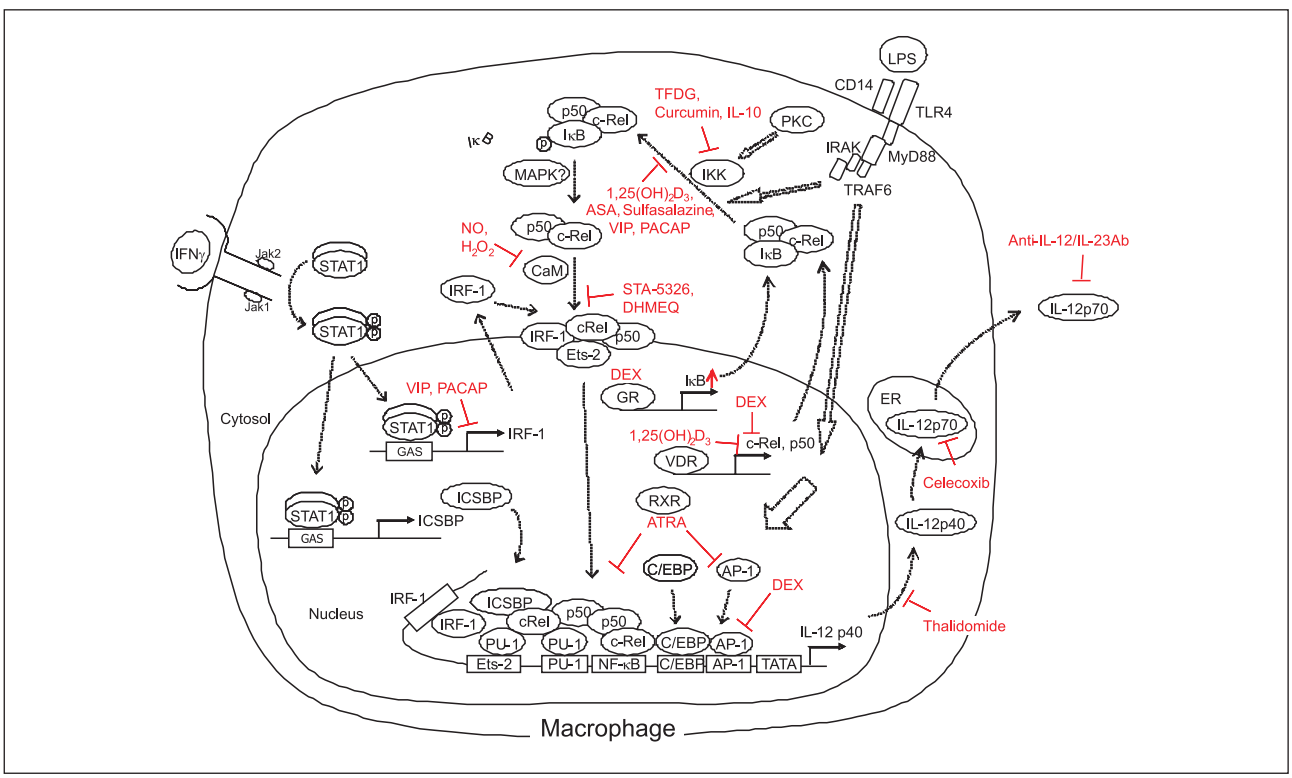


Fig. 1. IL-12 blockers and their sites of action.

Table I: Selectivity and potency of IL-12/IL-23 inhibitors.

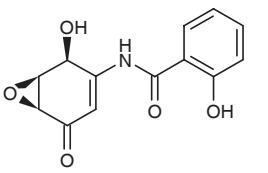
Inhibitor	Activity	Ref.
STA-5326	Inhibits IL-12 and IL-23 with IC_{50} values of < 20 nM; no significant suppression of other cytokines (IL-6, IL-1β and TNF-α)	53
	Reduces expression of IL-23p19 and IL-12/IL-23p40 and increases IL-10 in skin lesions of psoriasis patients	54
DHMEQ	Inhibits LPS-induced IL-6 and IL-12 at 1 μg/ml and above and IL-1β, TNF-α and NO less potently in RAW264.7 cells	57
1,25-Dihydroxyvitamin D_3	Inhibits IL-1β, IL-6 and TNF-α in LPS-stimulated PBMCs and GM-CSF and IL-12 in PHA-stimulated PBMCs at 10 nM or more; induces IL-10 in PMA/ionomycin-stimulated PBMCs at 100 nM and IL-5 in PHA-stimulated PBMCs at 10 nM or more	137
	Partially (50-70%) inhibits TNF-α produced by LPS-stimulated monocytes and macrophages; enhances the production of IL-10 but has little effect on IL-6 and IL-1β protein and mRNA production in LPS-stimulated PBMCs	138
all trans-Retinoic acid and 9-*cis*-retinoic acid	Inhibit TNF-α and IL-12p40 mRNA expression and potentiate IL-10 mRNA expression in LPS-stimulated THP-1 cells and cord blood mononuclear cells at 1 μM	76
	9-*cis*-Retinoic acid inhibits IL-12 in LPS-stimulated murine macrophages at 100 nM	74
	9-*cis*-Retinoic acid inhibits NO, TNF-α, IL-1β and IL-12p40 in LPS-stimulated microglia	73
Diltiazem	Inhibits IL-12 in LPS- and CD40L-stimulated DCs at 100 μM, with no effect on IL-10 production	90
	Increases IL-10 plasma concentrations in unstable angina patients with reduced IL-10 levels	139
Dantrolene	Inhibits IL-10, TNF-α and NO in LPS-stimulated RAW264.7 macrophages at 300 μM	92
	Suppresses LPS-induced plasma levels of IL-12, as well as TNF-α, IFN-γ and NO, and increases IL-10 levels at 20 mg/kg i.p. in BALB/c mice	91
Curcumin	Inhibits IL-12 with little effect on IL-10 in LPS-stimulated primary macrophages at 2.5 μg/ml and above	140
	Inhibits IL-12, IL-1β, IL-6 and TNF-α in LPS-stimulated murine bone marrow-derived DCs at 25 μM	141
Ciclosporin	Inhibits IL-12 but increases IL-10 in LPS-stimulated $CD11c^+$ DCs at 500 ng/ml	106
Salbutamol	Inhibits IL-12 in IFN-γ/LPS-stimulated human monocytes with an IC_{50} of 30 nM, but not IL-1α, IL-1β, IL-6 or IL-10	109
	Inhibits IFN-γ/LPS-induced IL-12 at 10 μM or more and TNF-α at 0.1 μM or more in murine macrophages	110
Pentoxifylline	Inhibits IL-12 and TNF-α in SAC-stimulated human PBMCs at 20 μg/ml and above, while enhancing IL-10; does not inhibit IL-12 in IFN-γ/SAC-stimulated human monocytes	111
Thalidomide	Inhibits IL-12 at 1 μg/ml and above and TNF-α and IL-10 at approximately 10-fold higher concentrations, with no effect on IL-6, in human PBMCs; does not inhibit IL-12 stimulated by IFN-γ priming	114
SM-735	Inhibits LPS- or PMA/ionomycin-induced IL-12, IFN-γ and IL-6 and concanavalin A (ConA)-induced IFN-γ in murine splenocytes at 1 μM	129
RDP-58	Inhibits ConA-induced TNF-α, IFN-γ and IL-12 *in vivo* at 20 mg/kg i.v. in mice	131
Celecoxib	Inhibits IL-12 secretion in 3H10-HEK cells producing IL-12 heterodimers at 20 μM	136

were treated orally with STA-5326, the expression of IL-23p19, IL-12/IL-23p40 and multiple downstream cytokines in the lesional skin was reduced following STA-5326 treatment in the highest dose group (54). In addition, STA-5326 increased the synthesis of the antiinflammatory cytokine IL-10 in the lesional skin, as well as in *in vitro* and *ex vivo* cultures of whole blood. At 12 weeks post-treatment, a reduction of skin-infiltrating T-cells (46% and 38%, respectively) and $CD11c^+$ DCs (78% and 52%, respectively) was observed in the epidermis and dermis in 17 responders of 47 evaluable patients from four tested cohorts. The clinical improvement achieved by orally administered STA-5326 was not sufficient for further clinical development at the dose levels tested.

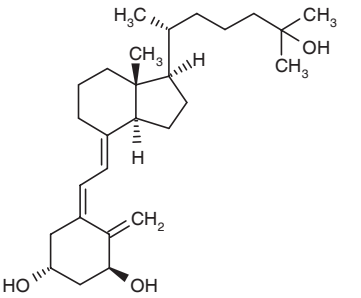
Dehydroxymethylepoxyquinomicin (DHMEQ, **2**), designed from the antibiotic epoxyquinomicin C (55), inhibits TNF-α-induced nuclear translocation of p65 in human Jurkat T-cells without affecting the phosphorylation and degradation of IκB (56). DHMEQ inhibits LPS-induced p65 nuclear translocation and secretion of IL-6, IL-12, IL-1β and TNF-α in murine macrophage RAW264.7 cells (57). The antiarthritic effect of subcutaneously injected DHMEQ was demonstrated *in vivo* in established CIA. In TNF-α-stimulated fibroblast-like synoviocyte cell lines established from rheumatoid arthritis patients, the activity of the NF-κB components p65 and p50 was inhibited by DHMEQ, leading to suppressed expression of the key inflammatory cytokine IL-6, CC chemokine ligand 2 (CCL2) and 5 (CCL5), matrix metalloproteinase 3 (MMP-3), intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) (58). No report has described the effect on c-Rel. DHMEQ is currently in preclinical evaluation.

1,25-Dihydroxyvitamin D_3 (1,25$[OH]_2D_3$, calcitriol; **3**), the hormonal form of vitamin D, is a multifunctional hormone acting mainly through the vitamin D receptor (VDR), a member of the nuclear receptor superfamily. Calcitriol is known to inhibit IL-12 by decreasing NF-κB binding to κB in the p40 promoter in THP-1 cells (59, 60). Calcitriol reduces the expression of p50 and c-Rel in activated human PBMCs (61) and c-Rel and RelB, but not p65, in bone marrow-derived mouse DCs (62), which possibly contributes to the reduced NF-κB activity upon IL-12 expression. In addition, a recent report showed that the half-life of IκBα mRNA increased with a parallel decrease in the phosphorylation of the protein, suggesting that increased IκBα levels leads to inhibition of the expression of inflammatory mediators (63). Because of hypercalcemia occurring after systemic application, its clinical application as an immunosuppressant has been hampered. 22-Ene-25-oxavitamin D (ZK-156979; **4**) is a vitamin D analogue with well-preserved immunosuppressive activity *in vitro* and reduced calcemic activity (64). Treatment with i.p. ZK-156979 reduced the severity of 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis in mice without exhibiting calcemic effects. Both early and late treatment abrogated body weight loss, diarrhea and macroscopic intestinal inflammation with a potency comparable to calcitriol (65). Analysis of lamina propria $CD4^+$ T-cells by Western blot showed a significant inhibition of IL-23, IL-17 and IL-6 protein expression (65, 66). Ro-26-2198 (**5**) is another vitamin D analogue that was shown to inhibit LPS-induced IL-12 and IFN-γ production *in vivo* in NOD mice following daily oral administration for 4 days before LPS injection (67). Over 10 vitamin D analogues are currently under active development for treating psoriasis, osteoporosis, prostate cancer or hyperparathyroidism.

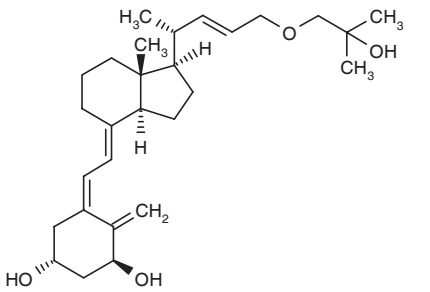
Dexamethasone (DEX; **6**), an antiinflammatory glucocorticoid, has been shown to inhibit IL-12p40 production in LPS-stimulated monocytes (68, 69). DEX inhibited *IL-12p40* gene transcription by inhibiting the activation of AP-1 and NF-κB transcription factors (44). DEX was shown to inhibit LPS-stimulated TNF-α in macrophages by induction of *IκBα* gene transcription and, as a consequence, by an increased rate of IκBα protein synthesis (70), which may also be involved in inhibition of IL-12. DEX most likely affects several transcriptional events via different modes of action (71), and the precise mecha-



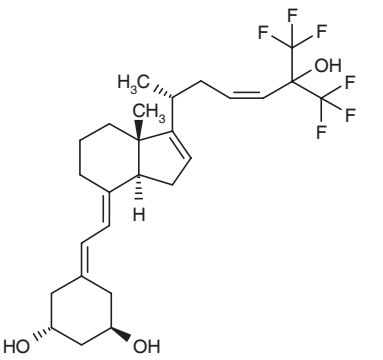
DHMEQ (**2**)



1,25-$(OH)_2D_3$ (**3**)



ZK-156979 (**4**)



Ro-26-2198 (**5**)

nism of IL-12 inhibition by DEX is not completely understood. Dehydroepiandrosterone (DHEA; **7**), a C19 adrenal steroid, decreases T-cell proliferation and the secretion of inflammatory cytokines, including IL-12p40, at least in part by inhibition of NF-κB activation (72).

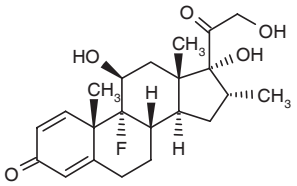
Retinoids, such as *all-trans*-retinoic acid (ATRA, tretinoin; **8**) and 9-*cis*-retinoic acid, inhibit LPS-stimulated production of IL-12 from mouse macrophages and primary mouse microglia (73, 74). Retinoid-mediated suppression of IL-12 production involves inhibition of NF-κB-DNA interactions through direct physical interactions of retinoid receptors with NF-κB (74). Alternatively, they can indirectly affect transcriptional regulation by inhibiting certain transcription factors such as AP-1 (75). Retinoic acid enhances the production of IL-10 while reducing the synthesis of IL-12 and TNF-α from LPS-stimulated monocytes/macrophages (76).

E-6060 (**9**) is a potent retinoic acid receptor α (RARα) subtype-selective retinoid agonist exerting stronger inhibition of LPS-induced mouse B-lymphocyte proliferation than ATRA (77). E-6060 significantly improved the survival rate and prevented the development of proteinuria in a mouse lupus nephritis model, associated with a decrease in serum IL-12p40 in mice (78).

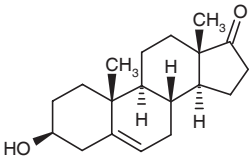
AM-80 (tamibarotene; **10**) is an RARα- and RARβ-specific (but not RARγ- and retinoid X receptor [RXR]) synthetic retinoid that is effective in the treatment of psoriasis and relapsed acute promyelocytic leukemia (APL) (79). AM-80 is approved in Japan for the treatment of APL. Phase III clinical trials for the treatment of APL in the United States are scheduled to start in 2007, and it holds fast track designation for the treatment of relapsed or refractory APL.

TAC-101 (**11**) is another synthetic retinoid selective for RARα. TAC-101 showed strong inhibition of the binding of AP-1 to DNA at 5 μM and above, while ATRA did not show any inhibition at 20 μM (80). TAC-101 reduced the swelling of forelimbs and hindlimbs and bone destruction in knee joints in a CIA model, associated with suppression of anti-type II collagen (CII) antibody production and delayed-type hypersensitivity (DTH) against CII. In addition, TAC-101 delayed the onset and development of EAE but did not affect the maximum symptoms of EAE in rats (81). TAC-101 is being evaluated in clinical trials for the oral treatment of hepatocellular carcinoma.

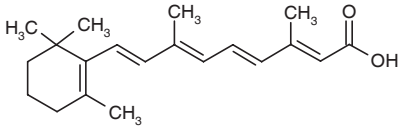
Acetylsalicylic acid (ASA; **12**) inhibits the secretion of the IL-12 heterodimer, as well as the p40 monomer, by human monocytic cells at concentrations of 1 mM and above through inhibition of NF-κB activation and binding to the p40 κB site in the p40 promoter (82). ASA prevents the degradation of IκB in activated Jurkat T-cells and the mouse PD31 pre-B-cell line (83), which may also occur in monocytes, leading to inhibition of NF-κB activation and subsequently IL-12 expression. Moreover, ASA and sodium salicylate inhibit IKK-β activity by binding to IKK-β to reduce ATP binding, suggesting that the reduced degradation of IκB is mediated in part by inhibition of IKK-β (84). Sulfasalazine (**13**), which contains 5-aminosalicylic acid, inhibits the LPS/IFN-γ-induced production of IL-12,



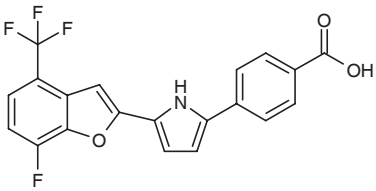
Dexamethasone (**6**)



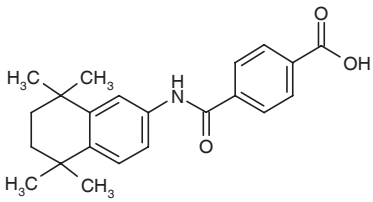
DHEA (**7**)



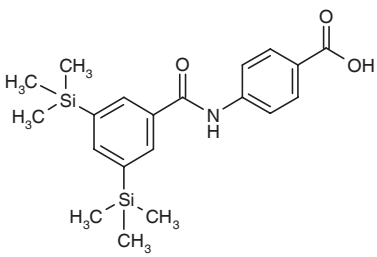
Tretinoin (**8**)



E-6060 (**9**)



AM-80 (**10**)



TAC-101 (**11**)

interfering with IκBα phosphorylation and thereby preventing nuclear translocation of NF-κB, in agreement with the reports for ASA (85, 86).

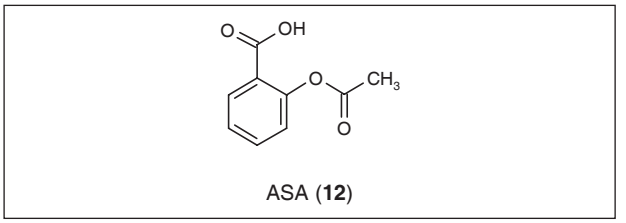
Diltiazem (**14**) is a calcium channel blocker that suppresses the activation of a variety of immune cells, such as T- and B-cells, NK cells, monocytes and DCs, and has been used in the treatment of cardiovascular disorders and the prevention of rejection after kidney transplantation. Diltiazem is reported to affect the maturation of human DCs (87) and the production of IL-12 and IFN-γ (88). Inhibition of the release of IL-6 by diltiazem in cardiopulmonary bypass in humans was also reported (89). The binding of the p65/p50 heterodimer to IL-12p35 and p40 κB was significantly reduced in DCs treated with LPS or CD40L in the presence of diltiazem, while the binding of the p50/p50 homodimer was slightly increased. The binding of c-Rel was not investigated. The slight increase in the binding of the p50/p50 homodimer may suggest that diltiazem reduced IL-12 expression in DCs, promoting the formation of the inhibitory p50/p50 complex that is associated with transcriptional repression (90). Currently, this agent is intended to be used in the cardiovascular field, but not for inflammation.

Dantrolene (**15**), another calcium channel blocker, was reported to reduce the LPS-induced increase in plasma levels of IL-12, as well as TNF-α, IFN-γ and NO, and to elevate IL-10 plasma levels at 20 mg/kg i.p. in mice (91, 92). In RAW264.7 cells, dantrolene reduced LPS-stimulated production of IL-10, in addition to TNF-α and NO (92).

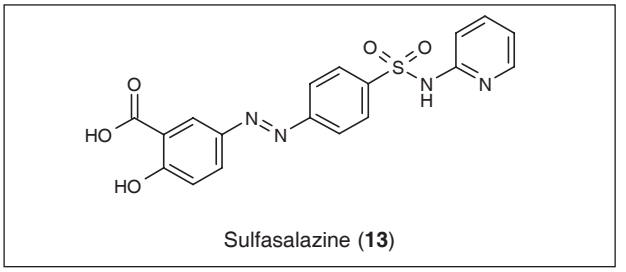
Curcumin, a component of the culinary spice turmeric, has been described as a potent antioxidant and antiinflammatory agent. Curcumin downregulates the expression of IL-12, as well as various proinflammatory cytokines, including TNF, IL-1, IL-2, IL-6, IL-8 and chemokines (93). Curcumin inhibits TNF-induced IKK and Akt activation, which blocks phosphorylation of IκBα and p65, leading to suppression of NF-κB activation and NF-κB-regulated gene expression (94).

Theaflavin-3,3'-digallate (TFDG), a tea polyphenol, is known to suppress the activation of NF-κB through inhibition of IKK activity (95). Oral administration of TFDG improved TNBS-induced colitis in association with decreased mRNA and protein levels of TNF-α, IL-12, IFN-γ and inducible NO synthase (iNOS) in colonic mucosa. TNBS-induced increases in nuclear localization of NF-κB and cytosolic IKK activity in colonic tissue were inhibited by TFDG pretreatment, suggesting that inhibition of NF-κB activation is involved in the inhibitory mechanism (96). No *in vitro* inhibitory activity against IL-12 has been reported.

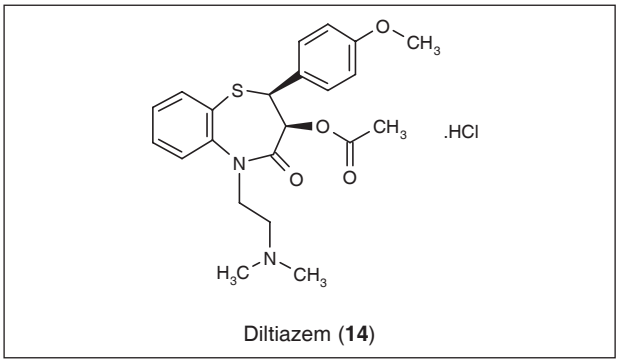
Two neuropeptides, vasoactive intestinal peptide (VIP) and the structurally related peptide pituitary adenylate cyclase-activating polypeptide (PACAP), have been shown to inhibit the production of TNF-α, IL-1β, IL-6 and NO by LPS-activated microglia, and mRNA levels of many proinflammatory cytokines, including IL-12p40 (97). VIP was also shown to downregulate IL-12 and IL-1β production, while increasing the production of IL-10 in LPS-



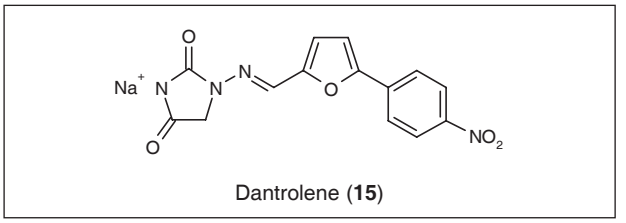
ASA (**12**)



Sulfasalazine (**13**)



Diltiazem (**14**)



Dantrolene (**15**)

stimulated XS106 cells, a DC cell line with characteristics of mature Langerhans cells (98). PACAP ameliorated both the clinical and pathological manifestations of MOG-induced EAE, and *in vitro* analysis revealed that PACAP suppressed the production of inflammatory cytokines, including TNF-α, IL-1β and IL-12, and the expression of the co-stimulatory factor B7-2 on macrophages and microglia (99). VIP and PACAP prevent the nuclear translocation of c-Rel by blocking IKK-mediated IκB phosphorylation and degradation, and also inhibit the synthesis of IRF-1, resulting in alterations in the Ets-2 binding complex on the p40 promoter (100). Both neuropeptides regulate the production of other proinflammatory cytokines by inhibiting p65 nuclear translocation (97). NAP, an 8-amino-acid neuroprotective peptide NAPVSIPQ —the smallest active element derived from the recently cloned activity-dependent neuroprotective protein (ADNP)— also downregulates IL-12, in addition to TNF-α and IL-16, in macrophages (101).

IL-10 is a potent inhibitor of IL-12 production, blocking the transcription of both p40 and p35 (102, 103). IL-10 inhibits LPS/IFN-γ-induced phosphorylation and degradation of IκBα, resulting in prevention of nuclear translocation of p65 (104) and c-Rel (105). Overexpression of c-Rel, but not p65, rescued the inhibitory effect of IL-10 on IL-12 production (105), suggesting the involvement of c-Rel in IL-10-mediated IL-12 regulation.

Ciclosporin, a potent calcineurin inhibitor, inhibits IL-12 production, while augmenting IL-10 production from LPS-stimulated human peripheral $CD11^+$ subsets (106). Although calcium and phosphatidylinositol 3-kinase (PI3K) signaling pathways have been shown to negatively regulate IL-12p40, as described earlier, LPS-induced IL-12p40 production in human monocytic cells was also reported to be positively regulated by the calcium pathway, in particular by CaM and CaM-dependent protein kinase II (CaMK-II)-activated PI3K. CaM/CaMK-II-activated PI3K and its downstream transcription factors NF-κB and AP-1 were downregulated by ciclosporin and FK-506, leading to inhibition of IL-12p40 transcription (107).

Other compounds under development that block IL-12 production (Fig. 1, Table I)

β_2-Adrenoceptor agonists

β_2-Adrenoceptor agonists are known to elevate intracellular cAMP (108). Salbutamol and other β_2-adrenoceptor agonists inhibit IL-12 production by human monocytes in response to LPS and DCs stimulated by CD40 (109). IL-1α, IL-1β, IL-6 or IL-10 production by LPS-stimulated monocytes is unaffected. Salbutamol also inhibits IL-12 and TNF-α in murine macrophages (110). IL-12 inhibition was dependent on β_2-adrenoceptor stimulation and correlated with increased levels of intracellular cAMP (109).

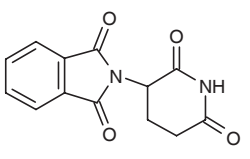
Phosphodiesterase inhibitors

Inhibitors of phosphodiesterase (PDE) that specifically hydrolyze cAMP to AMP reduce IL-12 production by elevating cAMP. Pentoxifylline is a general PDE inhibitor that is commonly used for the treatment of symptomatic vascular insufficiency because of its hemorrheological activity, and has also been used in the treatment of rheumatoid arthritis, multiple sclerosis and other immune-mediated disorders. Pentoxifylline inhibits the production of IL-12 and TNF-α from *Staphylococcus aureus* Cowan 1 (SAC)-stimulated PBMCs and enhances IL-10 and PGE_2 production (111). No significant decrease in IL-12 was observed for pentoxifylline in IFN-γ/SAC-stimulated human primary monocytes. Downregulation of IL-12 mRNA expression after treatment with pentoxifylline was observed in blood mononuclear cells from patients with relapsing-remitting multiple sclerosis (112). PDE4 is the predominant isoform in inflammatory and immune cells, and cilomilast, a selective PDE4 inhibitor, likewise inhibits LPS-induced IL-12 and TNF-α production by human PBMCs, with IC_{50} values of approximately 100 nM (113). Cilomilast is being evaluated for additional efficacy and safety, likely focusing on the sustainability of clinical benefits and long-term safety, before its final approval for asthma and chronic obstructive pulmonary disease (COPD).

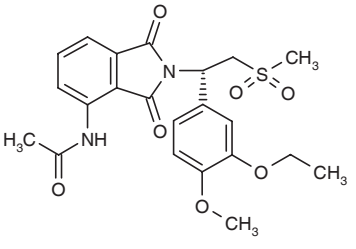
Thalidomide derivatives

Thalidomide (**16**) is a clinically effective compound that has shown activity in a wide variety of inflammatory and autoimmune diseases and cancer. Thalidomide is a known TNF-α production inhibitor, and also suppresses the production of IL-12 from human PBMCs and primary monocytes. When PBMCs were preincubated with IFN-γ, thalidomide lost the ability to suppress IL-12 (114). The production of TNF-α and IL-12 from LPMCs decreased during treatment with thalidomide, while the production of IL-1β and IL-6 did not change significantly (115). The accumulation of IL-12p40 and p35 mRNA was not significantly altered, suggesting that inhibition of IL-12 production by thalidomide occurs at least partially at the post-transcriptional level (114). Such a mechanism was also implicated in the suppression of TNF-α (116). Nuclear levels of NF-κB were found to be unaffected by thalidomide, further supporting the belief that the mechanism of action was not via inhibition of NF-κB (117, 118). In Jurkat cells, thalidomide was shown to block NF-κB activation induced by TNF-α and H_2O_2, but not NF-κB activated by LPS or phorbol ester, through a mechanism that involves inhibition of IκB kinase (119, 120), indicating that thalidomide cell- and stimulus-dependently acts on the NF-κB pathway.

The characterization of thalidomide analogues identified at least two distinct classes consisting of SelCIDs, which inhibit PDE4, and ImiDs, which do not inhibit PDE4 (121). CC-10004 (apremilast; **17**) is a representative of the SelCIDs that contains the phthalimide moiety of thalidomide, and is reported to decrease TNF-α, IL-12 and IFN-γ production *in vitro*. In an open-label pilot study



Thalidomide (**16**)



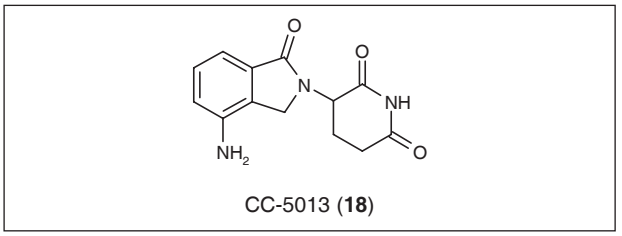
CC-10004 (**17**)

in patients with severe plaque-type psoriasis, CC-10004 provided a 20% reduction in epidermal skin thickness in 53% of patients, in association with decreases of 29% and 43%, respectively, in T-cells and of 28% and 25%, respectively, in $CD83^+$ cells in the epidermis and dermis (122). CC-10004 has been tested in randomized, double-blind phase II studies in psoriatic arthritis and psoriasis. The primary endpoint was achieved after 12 weeks of treatment, with 24% and 57% of patients receiving CC-10004 twice daily achieving PASI-75 and PASI-50 scores, respectively (123). The clinical development of CC-10004 in rheumatoid arthritis and other inflammatory diseases, in addition to psoriasis and psoriatic arthritis, is currently planned.

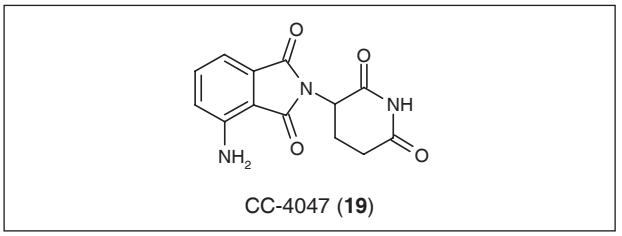
IMiDs have multiple mechanisms of action, which may result in both antiinflammatory and antitumor effects depending on the cell type and the stimulus involved. IMiDs inhibit IL-1α, IL-12 and IL-6 production and increase IL-10 production from LPS-stimulated PBMCs, while increasing TNF-α and IL-12 production and CD40L expression and decreasing IL-10 production in anti-CD3-stimulated PBMCs (124). Two IMiDs, CC-5013 (lenalidomide; **18**) and CC-4047 (pomalidomide; **19**), are considerably more potent with reduced side effects compared to thalidomide (125). CC-4047 reduced the levels of cyclooxygenase type 2 (COX-2) at the level of gene transcription and the production of prostaglandins (PG) in human LPS-stimulated monocytes (126). CC-5013 has been approved for myelodysplasia and multiple myeloma, and CC-4047 is undergoing phase II testing for the treatment of solid tumors and metastatic prostate cancer.

Artemisinin derivatives such as artesunate and artemether are the most effective antimalarial drugs currently available, and also demonstrate immunosuppressive activity in models of DTH (127, 128). SM-735, a semisynthetic artemisinin derivative and nonsteroidal antiinflammatory drug, inhibits IL-12, IFN-γ and IL-6 induced by LPS or PMA plus ionomycin, and suppresses both DTH and B-cell-mediated quantitative hemolysis of sheep red blood cells (129). Artemether impairs both antigen- and anti-CD3-induced phosphorylation of ERK, and anti-CD3-induced phosphorylation of Raf1 and activation of Ras in primary T-cells, suggesting that the mechanism of immunosuppressive activity in T-cells involves inhibition of the activation of the Ras-Raf1-ERK1/2 protein kinase cascade (130). There is no information regarding its site of action in monocyte lineage cells.

RDP-58, a peptide derived from the human leukocyte antigen class I heavy chain, disrupts Toll-like and TNF receptor family-mediated signals. RDP-58 inhibits TNF-α, IFN-γ and IL-12 synthesis in human and murine macrophage cell lines *in vitro* and their production *in vivo* in mice (131, 132). Topical application of RDP-58 in mice ameliorated 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced irritant contact dermatitis, with substantial reductions in skin thickness and tissue weight, neutrophil-mediated myeloperoxidase activity, inflammatory cytokine production and various histopathological indicators (133). RDP-58 neither prevented acute graft-versus-host disease nor significantly prolonged survival of allogeneic hematopoietic cell transplantation recipients in a canine model (134). RDP-58 does not affect TNF-α mRNA steady-state levels, but inhibits protein synthesis (131) and also inhibits the phosphorylation of p38 MAPK and JNK1/JNK2 kinases and the binding and transcriptional activity of NF-κB and AP-1, suggesting effects at both the transcriptional and translational levels (132). Although RDP-58 has shown promising results in mild to moderate ulcerative colitis (135), there seem to be no ongoing clinical trials of the agent.



CC-5013 (**18**)



CC-4047 (**19**)

Celecoxib inhibits the secretion of dimeric IL-12p70 and p40 with identical IC_{50} values. This activity appears to be independent of COX inhibition, as indomethacin, a potent inhibitor of prostaglandin synthesis, does not inhibit IL-12 production. The effect was not due to a blockade of transcription, suggesting a post-transcriptional effect of celecoxib on IL-12 folding in the endoplasmic reticulum (136).

Conclusions

The recent successful clinical studies with anti-IL-12/IL-23 antibodies confirm IL-12/IL-23 as an attractive target and reinforce the therapeutic potential of oral small-molecule IL-12/IL-23 blockers. A number of compounds have been reported to block the production of IL-12. However, the selectivity and potency of most compounds do not appear to be sufficient for clinical benefit. Most of the inhibitors are not selective for IL-12 and inhibit other cytokines, such as TNF-α and IL-6, mainly due to their action on common targets that regulate numerous cytokines, such as p65/p50 NF-κB and IκB. Many of the studies elucidating the mechanism of the inhibitory activity have focused on the effects on NF-κB p65 rather than c-Rel, the dominant form of NF-κB for regulating IL-12. Some of the blockers require high concentrations to inhibit IL-12 compared to other cytokines, indicating the possibility that the effect on c-Rel is weaker than the observed effect on p65, and that the inhibitory activity is derived from the effect on p50, the subunit that forms a heterodimer with c-Rel. Furthermore, it should be noted

that inhibition was mostly demonstrated against LPS-stimulated IL-12 production. However, pentoxifylline and thalidomide lose their suppressive effects on IL-12 production when cells are primed with IFN-γ. This type of drugs might not be as effective when used alone for Th1-mediated chronic autoimmune or immunological disorders that are characterized by recurrently high levels of IFN-γ. Lastly, the inhibition is frequently cell type- and stimulus-dependent, emphasizing the importance of the analysis of *in vivo* IL-12 levels. However, there are only a few reports demonstrating inhibition *in vivo*, partially because of the difficulty in detecting the local and transient production of this harmful inflammatory cytokine.

It is remarkable that most of the small-molecule compounds that inhibit IL-12 enhance IL-10 production regardless of the differences in their mechanisms of action. The enhancement of IL-10 by IL-12 blockers is observed *in vitro* simultaneously with and not secondary to the suppression of IL-12. The trend is consistently observed *in vivo*, primarily in animal models of immune diseases. Recent human clinical biomarker studies have shown an increase in IL-10 by IL-12 blockers such as STA-5326 in skin lesions of psoriasis patients. The lack of an increase in IL-10 in the skin lesions with anti-IL-12 antibodies indicates that the increase in IL-10 is not the result of IL-12 inhibition. These results indicate a reciprocal regulation of the expression of these two proteins. Considering the critical role of the inflammatory IL-12 cytokine and the antiinflammatory IL-10 cytokine, the dual effect by IL-12 blockers is expected to add benefit to the clinical outcome.

It is not clearly understood how the regulation of IL-12 expression is distinct from the regulation of other cytokines. In fact, most of the reported IL-12 transcription blockers simultaneously inhibit other inducible cytokines because of their common mechanisms of action in regulating cytokines regardless of proximity to the activation of the promoters. Understanding the precise regulation of IL-12/IL-23 and the differences in regulation compared to other genes is essential in order to develop IL-12/IL-23-selective blockers. Recent findings of a critical role for c-Rel in the regulation of IL-12/IL-23p40 and IL-23p19 suggest that c-Rel inhibition may be an attractive strategy to differentiate IL-12/IL-23-selective blockers from other compounds that inhibit a wide variety of inflammatory mediators. Although few reports describe the effects of compounds on IL-23 at the protein level, IL-12 blockers that downregulate the shared p40 subunit are expected to inhibit the production of both IL-12 and IL-23. Little is known about the regulation of IL-23p19 expression and the similarities and differences relative to p40 expression. It is of interest to determine whether selective blockade of IL-23, without affecting IL-12, is sufficient for efficacy, or whether dual blockade of both IL-12/Th1 and IL-23/Th17 pathways is essential for a meaningful clinical outcome. The risk of increasing opportunistic infections by suppressing IL-12 and IL-23, which are critical for the clearance of certain pathogens, also needs to be considered. These questions will be answered shortly through studies with anti-IL-12/IL-23p40 and anti-IL-23p19 antibodies.

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