IL-23/IL-17A Dysfunction Phenotypes Inform Possible Clinical Effects from Anti-IL-17A Therapies

Andrew Blauvelt1, Mark G. Lebwohl2 and Robert Bissonnette3

Biologics that neutralize specific cytokines have improved outcomes for several immune-mediated disorders but may also increase risks for particular side effects. This article postulates potential immunologic consequences of inhibiting components of the IL-23/T-helper cell 17 pathway—the target of next-generation biologics for treating psoriasis—based on clinical phenotypes of inherited or acquired deficiencies in this pathway. Generally, downstream deficiencies (e.g., IL-17A, IL-17F) are associated with fewer disorders compared with upstream deficiencies, suggesting that selectively blocking downstream targets may result in a narrower range of side effects. However, safety of these specific inhibitions must be established in long-term studies.

Journal of Investigative Dermatology (2015) 135, 1946–1953; doi:10.1038/jid.2015.144; published online 14 May 2015

INTRODUCTION

Imbalances in cytokine levels have been implicated in the pathogenesis of a variety of diseases (O’Shea et al., 2002). For disorders in which cytokines are upregulated, such as psoriasis and rheumatoid arthritis, biologic agents that neutralize specific cytokines have improved treatment outcomes while decreasing side effects (Kim and Solomon, 2010; Focosi et al., 2011). Such drugs act therapeutically by modulating abnormal immune responses caused by aberrant cytokine levels. An unintended consequence, however, is that these therapies may also inhibit normal host defenses that utilize the targeted cytokine (Kim and Solomon, 2010; Chu, 2013).

Clinical improvements observed in patients with psoriasis and rheumatoid arthritis treated with tumor necrosis factor-α inhibitors have inspired researchers to study novel cytokine targets with the goal of maximizing therapeutic efficacy while minimizing side effects (Nwe et al., 2013). Targeting these cytokines may alleviate safety concerns resulting from upstream cytokine inhibition and inhibition at multiple points in the inflammatory cascade (Bongartz et al., 2006; Leombruno et al., 2009). As understanding of the pathogenesis of inflammatory and immune-mediated diseases has improved, cytokines involved in the IL-23/T-helper cell (Th17) pathway have been identified as key modulators of adaptive immune responses associated with the initiation, progression, and maintenance phases of these diseases (Blauvelt, 2008; Kellner, 2013; Qu et al., 2013). Therefore, there is a strong rationale for targeting cytokines in this pathway (Figure 1a).

Because antimicrobial peptides partially triggered by the IL-23/Th17 pathway are involved in mucocutaneous defense against bacterial and fungal pathogens, therapeutic targeting of this cytokine may increase susceptibility to these infections (Waite and Skokos, 2012; Bedoya et al., 2013; Kellner, 2013). Hence, this article will review the role of the IL-23/Th17 pathway in the pathogenesis of immune-mediated disorders and explore potential immunologic consequences of inhibiting members of this pathway. The principal method for understanding the immunologic consequences of disrupting the IL-23/Th17 pathway will be to examine clinical phenotypes associated with pathway deficiencies, which may occur because of genetic mutations affecting the production or activation of a specific cytokine or its receptor or because of the production of autoantibodies against endogenous cytokines.

ROLE OF THE IL-23/TH17 PATHWAY IN THE PATHOGENESIS OF PSORIASIS AND OTHER IMMUNE-MEDIATED DISEASES

In patients with psoriasis, Th17 cells are elevated in cutaneous lesions and blood, as are the messenger RNA and protein levels of IL-23, IL-17A, IL-17F, IL-22, and IL-21 (Di Cesare et al., 2009; Kagami et al., 2010; Michelak-Stoma et al., 2011; Yilmaz et al., 2012; Nwe et al., 2013). These findings suggest that Th17 cells and associated cytokines are important pathogenic mediators of psoriasis (Hueber et al., 2010). The IL-23/Th17 pathway model postulates that, in response to a specific trigger, specific cells produce tumor necrosis factor-α, IL-1β, IFN-α, and IL-6 in susceptible individuals (Lynde et al., 2014). These cytokines stimulate myeloid dendritic cells to produce IL-23, which promotes Th17 cell differentiation, proliferation, and maintenance (Rizzo et al., 2011; Lynde et al., 2014). Th17 cells migrate to the skin and become activated via the signal transduction protein signal transducer
Figure 1. Role of cytokines in psoriasis pathophysiology and immune defense against infections. (a) Pathophysiology of psoriasis, with indications for the relative positions of key cytokines and their inhibitors. (b) Signaling pathways associated with specific increases in susceptibility to pathogens. HSV, herpes simplex virus; NEMO, NF-kappaB essential modulator; STAT, signal transducer and activator of transcription; TIR, Toll-like receptor/IL-1 receptor; TNF-R, tumor necrosis factor receptor; TYK, tyrosine kinase (Bustamante et al., 2008). Adapted from Bustamante et al., 2008, with permission from Elsevier.
and activator of transcription 3 (STAT3) to produce IL-17A, IL-17F, and IL-22; along with several chemokines. In addition, IL-17-, IL-21-, and IL-22-producing CD8+ T cells have been observed in psoriatic plaques and implicated in the pathogenesis of psoriasis (Ortega et al., 2009; Res et al., 2010). Together, these cytokines and chemokines drive chronic inflammation associated with psoriatic lesion formation, including keratinocyte activation and hyperproliferation. Activated keratinocytes, in turn, produce many of the same pro-inflammatory mediators that initiate the psoriasis cascade, thereby creating a self-perpetuating cycle that leads to persistence of psoriatic plaques (Di Cesare et al., 2009; Harper et al., 2009; Gaffen, 2011; Girolomoni et al., 2012; Nwe et al., 2013).

**Mendelian susceptibility to mycobacterial disease (MSMD)**
Mendelian susceptibility to mycobacterial disease is a rare syndrome with clinical symptoms resulting from infection with mildly virulent bacteria (Fieschi et al., 2003 and 2004). Although early descriptions of MSMD suggested that infection susceptibility was usually limited to *Mycobacterium* and *Salmonella* (Fieschi and Casanova, 2003; Fieschi et al., 2003 and 2004), more recent studies have shown that *Candida* infections are not uncommon (~25% of patients), and *Klebsiella pneumonia* infection, paracoccidioidomycosis, and leishmaniasis have also been reported (Ouederni et al., 2014; Ramirez-Alejo et al., 2014). Most *Candida* infections in this population are isolated oropharyngeal candidiasis, and risk of systemic infection is low (Fieschi and Casanova, 2003; Ouederni et al., 2014). Patients with MSMD do not exhibit increased susceptibility to common viral pathogens, suggesting that their immune system is not broadly compromised (Fieschi and Casanova, 2003). However, the prognosis for MSMD varies, ranging from complete recovery to premature mortality (Ramirez-Alejo et al., 2014).

To date, nine mutations have been associated with MSMD; the clinical phenotypes of MSMD can vary depending on the nature of the underlying genetic mutation (Bustamante et al., 2008; Ouederni et al., 2014; Ramirez-Alejo et al., 2014). Mutations in IL12RB1, which encodes a common subunit of the IL-12 and IL-23 receptor, can cause profound defects in

| Clinical presentation | Known defects associated with disease | Effects on IL-17, IL-23, and closely related cytokines |
|-----------------------|---------------------------------------|-------------------------------------------------------|
| MSMD                  | IL12RB1 mutation                      | Impaired IFN-γ-mediated immunity                       |
|                       | IL12B mutation                        |                                                        |
|                       | IFNGR1 mutation                       |                                                        |
|                       | STAT1 mutation                        |                                                        |
|                       | IL-12/23p40 deficiency                |                                                        |
|                       | IL-12Rβ1 deficiency                  |                                                        |
| *Tuberculosis* infection | IL12RB1 mutation                      | Reduced production of IFN-γ                           |
| *Salmonella* infection | IL-23R deficiency                     | Depletion of Th17 cells and IL-17A/F results in reduced immunoprotective effects |
|                       | IL-12/23p40 deficiency                |                                                        |
|                       | IL-12Rβ1 deficiency                  |                                                        |
| CMC disease (associated with *C. albicans* infection) | IL-17RA deficiency | Reduced production of IL-17A, IL-17F, IL-22, and IFN-γ weaken epithelial mucosal barriers |
|                       | IL-17F deficiency                     |                                                        |
|                       | STAT1 GOF mutation                    |                                                        |
|                       | CARD9 mutation                        |                                                        |
|                       | Dectin-1 LOF mutation                 |                                                        |
| APECED (APS-1)        | AIRE mutation                         | High levels of autoantibodies to IL-17F, IL-22, and IL-17A |
| HIES (Job’s syndrome) | STAT3 mutation (AD)                   | Reduced differentiation of Th17 cells and production of IL-17A |
|                       | DOCK8 mutation (AR)                   |                                                        |

Abbreviations: AD, autosomal dominant; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome; APS-1, autoimmune polyendocrinopathy syndrome type 1; AR, autosomal recessive; CMC, chronic mucocutaneous candidiasis; GOF, gain-of-function; HIES, hyper-IgE syndrome; LOF, loss-of-function; MSMD, Mendelian susceptibility to mycobacterial disease; Th, T-helper cell.

**PHENOTYPIC PRESENTATION OF CYTOKINE OR RECEPTOR DEFICIENCIES IN THE IL-23/TH17 PATHWAY**
Several unique defects have been identified in genes that encode for components of the IL-23/Th17 pathway. These genetic mutations result in a number of rare, complex human diseases associated with either cytokine or receptor deficiencies or with autoantibody production. Common consequences of these disorders are increased susceptibility to pathogens due to changes in host defense. Table 1 provides a summary of findings on human diseases associated with defects in IL-23/Th17 function; descriptions of the phenotypic presentations of these diseases follow.
IL-12 and IL-23 signaling (van de Vosse et al., 2013) and are the most common cause of MSMD (Bustamante et al., 2008; Ouederni et al., 2014). Patients with IL-12Rβ1 or IL-12/23p40 deficiencies are more susceptible to salmonellosis and mild forms of candidiasis compared with patients with MSMD caused by other mutations (Bustamante et al., 2008; Ouederni et al., 2014). IFNGR1, IFNGR2, and STAT1 mutations directly affect IFN-γ-mediated immune responses, and the level of impairment in IFN-γ function is correlated with clinical phenotype (i.e., patients with only partially impaired IFN-γ responses have milder disease; Bustamante et al., 2008; Boisson-Dupuis et al., 2012). The STAT1 mutations observed in patients with MSMD are autosomal-dominant loss of function and are associated with generally mild disease (Boisson-Dupuis et al., 2012).

Tuberculosis
Mutations in IL12RB1 are also associated with increased susceptibility to tuberculosis in humans (Altare et al., 1998; Akahoshi et al., 2003; Al-Muhsen and Casanova, 2008; de Beaucoudrey et al., 2010). It has been hypothesized that these IL12RB1 polymorphisms may reduce receptor responsiveness to IL-12 (and possibly IL-23), thereby disrupting IFN-γ-mediated immunity (Akahoshi et al., 2003). Animal models have also shown that TLR2-deficient mice infected with M. tuberculosis TLR2 have significantly decreased Th17 cell counts, IL-17 expression, and IL-23p19 expression (Teixeira-Coelho et al., 2011). Similarly, polymorphisms in TLR2 and TLR2-signaling molecules have been associated with increased susceptibility to tuberculosis infection in humans (Teixeira-Coelho et al., 2011). Observed IL-17A deficiencies are probably of limited importance in host defense against tuberculosis infection, as IL-22 has been shown to be the key Th17 effector cytokine in pulmonary host defense mechanisms (Ajula et al., 2008), and depletion of IL-17A-producing CD4+ T cells has been shown to have little to no effect on disease progression during primary M. tuberculosis infection (Khadar et al., 2005).

Salmonella
Nontyphoidal Salmonella (NTS) infections can cause localized, albeit potentially severe, gastroenteritis in immunocompetent individuals. However, when immunocompromised individuals are exposed to NTS, the pathogen can spread beyond the intestines to the bloodstream, resulting in a life-threatening condition known as NTS bacteremia (Raffatellu et al., 2008; Godinez et al., 2011). Studies in humans have linked IL-12/IL-23-component deficiencies to increased susceptibility to severe extra-intestinal NTS infection; however, it was not specified which genes were affected in these patients (MacLennan et al., 2004). The protective role of these cytokines against Salmonella appears to be independent of the IFN-γ immune response (MacLennan et al., 2004). Rather, it is suggested that the IL-23/Th17 pathway has a key role in mucosal inflammatory responses to NTS infection (Godinez et al., 2011).

Chronic mucocutaneous candidiasis (CMC)
Severe acquired immunodeficiencies (e.g., uncontrolled HIV or Severe Combined Immunodeficiency) or genetic defects in the IL-23/Th17 pathway can increase patients’ susceptibility to a number of syndromes that are all associated with chronic or recurrent mucosal or skin infections with Candida albicans (Table 1; Puel et al., 2010b; Hanna and Etzioni, 2011; Huppler et al., 2012). These syndromes are collectively referred to as CMC (Hanna and Etzioni, 2011). CMC manifests as superficial lesions on the skin, nails, and mucosal surfaces that often respond poorly to antifungal therapy (Puel et al., 2010b; Hanna and Etzioni, 2011). Clinical presentations and severities of CMC are variable, even between family members with the same genetic mutations (Cárdenes et al., 2010; Boisson-Dupuis et al., 2012; Lilic, 2012). Subtypes of CMC include the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED), autosomal-dominant CMC with or without thyroid disease, and isolated CMC disease (van de Veerendonk et al., 2011). Across the subtypes of CMC, IL-22 has been identified as a dominant cytokine in providing protective immunity against candidiasis (De Luca et al., 2010; Kisand et al., 2010). IL-17A and IL-17F are also natural defenders against CMC, but studies have suggested that these cytokines may be less critical compared with IL-22 in mucosal host-defense mechanisms (De Luca et al., 2010; Kisand et al., 2010 and 2011).

Another key modulator of human mucosal antifungal defense is the β-glucan receptor, dectin-1. In a study of family members affected by chronic vulvovaginal candidiasis or onychomycosis, Ferwerda and colleagues identified stop-codon mutations in dectin-1 that were associated with reduced production of IL-17, tumor necrosis factor-α, and IL-6 (Ferwerda et al., 2009). However, neutrophil function is preserved in patients with dectin-1 deficiencies, resulting in protection against invasive fungal infections (Ferwerda et al., 2009).

Cytokine autoantibodies linked to APECED. APECED, also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED), autosomal-dominant CMC with or without thyroid disease, and isolated CMC disease (van de Veerendonk et al., 2011). Across the subtypes of CMC, IL-22 has been identified as a dominant cytokine in providing protective immunity against candidiasis (De Luca et al., 2010; Kisand et al., 2010). IL-17A and IL-17F are also natural defenders against CMC, but studies have suggested that these cytokines may be less critical compared with IL-22 in mucosal host-defense mechanisms (De Luca et al., 2010; Kisand et al., 2010 and 2011).

Another key modulator of human mucosal antifungal defense is the β-glucan receptor, dectin-1. In a study of family members affected by chronic vulvovaginal candidiasis or onychomycosis, Ferwerda and colleagues identified stop-codon mutations in dectin-1 that were associated with reduced production of IL-17, tumor necrosis factor-α, and IL-6 (Ferwerda et al., 2009). However, neutrophil function is preserved in patients with dectin-1 deficiencies, resulting in protection against invasive fungal infections (Ferwerda et al., 2009).

Cytokine autoantibodies linked to APECED. APECED, also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED), autosomal-dominant CMC with or without thyroid disease, and isolated CMC disease (van de Veerendonk et al., 2011). Across the subtypes of CMC, IL-22 has been identified as a dominant cytokine in providing protective immunity against candidiasis (De Luca et al., 2010; Kisand et al., 2010). IL-17A and IL-17F are also natural defenders against CMC, but studies have suggested that these cytokines may be less critical compared with IL-22 in mucosal host-defense mechanisms (De Luca et al., 2010; Kisand et al., 2010 and 2011).

Another key modulator of human mucosal antifungal defense is the β-glucan receptor, dectin-1. In a study of family members affected by chronic vulvovaginal candidiasis or onychomycosis, Ferwerda and colleagues identified stop-codon mutations in dectin-1 that were associated with reduced production of IL-17, tumor necrosis factor-α, and IL-6 (Ferwerda et al., 2009). However, neutrophil function is preserved in patients with dectin-1 deficiencies, resulting in protection against invasive fungal infections (Ferwerda et al., 2009).

Cytokine autoantibodies linked to APECED. APECED, also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED), autosomal-dominant CMC with or without thyroid disease, and isolated CMC disease (van de Veerendonk et al., 2011). Across the subtypes of CMC, IL-22 has been identified as a dominant cytokine in providing protective immunity against candidiasis (De Luca et al., 2010; Kisand et al., 2010). IL-17A and IL-17F are also natural defenders against CMC, but studies have suggested that these cytokines may be less critical compared with IL-22 in mucosal host-defense mechanisms (De Luca et al., 2010; Kisand et al., 2010 and 2011).

Another key modulator of human mucosal antifungal defense is the β-glucan receptor, dectin-1. In a study of family members affected by chronic vulvovaginal candidiasis or onychomycosis, Ferwerda and colleagues identified stop-codon mutations in dectin-1 that were associated with reduced production of IL-17, tumor necrosis factor-α, and IL-6 (Ferwerda et al., 2009). However, neutrophil function is preserved in patients with dectin-1 deficiencies, resulting in protection against invasive fungal infections (Ferwerda et al., 2009).

Cytokine autoantibodies linked to APECED. APECED, also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED), autosomal-dominant CMC with or without thyroid disease, and isolated CMC disease (van de Veerendonk et al., 2011). Across the subtypes of CMC, IL-22 has been identified as a dominant cytokine in providing protective immunity against candidiasis (De Luca et al., 2010; Kisand et al., 2010). IL-17A and IL-17F are also natural defenders against CMC, but studies have suggested that these cytokines may be less critical compared with IL-22 in mucosal host-defense mechanisms (De Luca et al., 2010; Kisand et al., 2010 and 2011).

Another key modulator of human mucosal antifungal defense is the β-glucan receptor, dectin-1. In a study of family members affected by chronic vulvovaginal candidiasis or onychomycosis, Ferwerda and colleagues identified stop-codon mutations in dectin-1 that were associated with reduced production of IL-17, tumor necrosis factor-α, and IL-6 (Ferwerda et al., 2009). However, neutrophil function is preserved in patients with dectin-1 deficiencies, resulting in protection against invasive fungal infections (Ferwerda et al., 2009).
IL-22 (Liu et al., 2011; van de Veerdonk et al., 2011; Cypowyj et al., 2012; Huppler et al., 2012). Several different STAT3 gain-of-function missense mutations also have been identified, but the link between the type of mutation and clinical presentation is not well defined. However, complete STAT3 deficiency is thought to be associated with more severe infectious phenotypes (Boisson-Dupuis et al., 2012).

Isolated CMC. Isolated CMC is commonly referred to as CMC disease (Cypowyj et al., 2012). CMC disease without any other known phenotype has been observed in patients with a complete autosomal-recessive deficiency in the receptor IL-17RA (due to mutations in the IL17RA gene) or autosomal-dominant mutations in IL17F (Cypowyj et al., 2012; Puel et al., 2011). Genetic mutations in IL-17RA result in a lack of cellular response to IL-17A, IL-17F, IL-17A/IL-17F, IL-17C, and IL-17E (also known as IL-25; Cypowyj et al., 2012; Puel et al., 2011).

Caspase recruitment domain-containing protein 9 (CARD9) is a signal transducer found in the cytosol of myeloid cells that is required for induction of Th17 cells (Huppler et al., 2012; Drewniak et al., 2013). Isolated CMC has also been observed in patients with autosomal-recessive CARD9 mutations. The CMC phenotype in CARD9-deficient patients tends to be more severe, and cases of invasive CNS and brain candidiasis have been reported (Puel et al., 2010b; Huppler et al., 2012; Drewniak et al., 2013; Sillevis Smitt and Kuijpers, 2013, 2014). Some studies have suggested that susceptibility to CMC in CARD9-deficient individuals results from impaired dectin-1 signaling (Hanna and Etzioni, 2011). However, recent studies have shown that neutrophil-killing defects may be responsible for allowing more invasive forms of CMC to progress (Drewniak et al., 2013).

**Hyperimmunoglobulin E syndrome**

The Hyperimmunoglobulin E syndrome (HIES, Job’s syndrome) is a rare primary immunodeficiency that can result in severe atopic dermatitis, pneumatocele formation, connective tissue and skeletal abnormalities, and recurrent skin and lung infections (Hanna and Etzioni, 2011; Szczawinska-Poplonyk et al., 2011). Cutaneous and pulmonary staphylococcal infections and CMC are also observed in the majority of patients with HIES (Puel et al., 2010b; Hanna and Etzioni, 2011). In addition, serum IgE levels are markedly elevated to 10–100 times normal range (Ma et al., 2008; Hanna and Etzioni, 2011).

Autosomal-dominant HIES is caused by dominant-negative mutations in STAT3 (Ma et al., 2008; Zelante et al., 2009; Hanna and Etzioni, 2011). These mutations result in decreased expression of regulator retinoid-related orphan receptor γt, which is a transcription factor required for IL-17 expression; thus, IL-17A production is greatly reduced (Ma et al., 2008). Reductions in IL-1β, IL-6, IL-21, and IL-23-induced differentiation of naïve CD4+ T cells into Th17 cells result in lower Th17 cell counts and contribute to reductions in IL-17 and IL-22 expression (Ma et al., 2008; Schimke et al., 2010; Huppler et al., 2012; Puel et al., 2012). Different STAT3 mutations are associated with different levels of impairment in IL-17 production and varying disease severity. For example, IL-17 production was found to be completely absent in patients with R382W or V463del STAT3 mutations, whereas patients with STAT3 linker domain mutations produced measureable amounts of IL-17 and had milder disease (van de Veerdonk et al., 2010).

Another distinct disorder, autosomal-recessive HIES, has been observed in patients with deficiencies in dedicator of cytokinesis 8, which results in impaired T-cell activation and memory (Schimke et al., 2010; Huppler et al., 2012; Lilic, 2012). In addition, dedicator of cytokinesis 8 regulates actin, which may explain the skeletal abnormalities observed in patients with HIES (Szczawinska-Poplonyk et al., 2011). Isolated cases of autosomal-recessive HIES have also been observed in patients with TYK2 deficiencies, suggesting that defects in Janus kinase signaling may also be associated with certain forms of HIES (Minegishi and Karasuyama, 2009; Schimke et al., 2010; Lilic, 2012). Such deficiencies are further upstream in the IL-23/Th17 pathway, as Janus kinases phosphorylate STATs (Minegishi and Karasuyama, 2009). The clinical features of autosomal-recessive HIES are similar to autosomal-dominant HIES, but patients with the recessive form may be more susceptible to severe fungal and viral infections, as well as asthma, food allergies, and malignancies (Szczawinska-Poplonyk et al., 2011; Huppler et al., 2012). Patients with DOCK8 mutations are less likely to present with certain cutaneous symptoms, such as newborn eczematous eruptions, which are more common in patients with autosomal-dominant HIES caused by STAT3 mutations (Sillevis Smitt and Kuijpers, 2013).

**DISCUSSION**

Several diseases can manifest as a result of inherent or acquired deficiencies in cytokines or their receptors. Examination of the clinical phenotypes from these diseases may provide insights into potential side effects for therapies that target these cytokines. Several important caveats should be noted: importantly, anticytokine therapy is not expected to mimic cytokine-signaling pathway mutations, in which the development of these diseases is likely to be affected by lifelong (and sometimes complete) depletion in cytokine levels. Thus, the genetic diseases discussed herein are not expected to mirror what would be observed during biologic therapy for immune-mediated disorders. Furthermore, current anticytokine therapy does not impair production of the targeted cytokine and thus does not result in complete and, more importantly, permanent loss of function. These distinctions are critical because the extent of functional deficiencies in rare diseases identified here corresponds to the extent of the clinical phenotypes (van de Veerdonk et al., 2010). For example, in patients with HIES, partial IL-17 deficiency is associated with a milder clinical phenotype compared with complete IL-17 deficiency (van de Veerdonk et al., 2010). Similarly, in most of the genetic disorders discussed, many different cytokines are altered simultaneously and thus are highly dissimilar to single-cytokine depletion mediated by a biologic.

Long-term favorable clinical outcomes are possible for many patients with genetic deficiencies in the IL-23/Th17 pathway because of redundancies in host-defense mechanisms and
because deficiencies in a single cytokine or its receptor generally do not lead to widespread disease susceptibility (Fieschi et al., 2003; Godinez et al., 2011). For example, although early studies postulated that IL-12 production by phagocytes and antigen-presenting cells was a key component of both innate resistance and adaptive immune responses (Trinchieri, 1995), Fieschi and colleagues later found that deficiencies in IL-12 or its receptor do not increase susceptibility to a wide range of infections (Fieschi and Casanova, 2003; Fieschi et al., 2003). Instead, consequences of these deficiencies are usually limited to MSMD, whereas defenses against other microorganisms remain intact, and risk for serious systemic infection remains low (Fieschi and Casanova, 2003; Fieschi et al., 2003). Similarly, studies examining susceptibility to NTS bacteremia have concluded that, although IL-17A has a key role in protecting ileal mucosa, isolated deficiencies in this cytokine are unlikely to result in substantially increased risk for systemic Salmonella infection because the antimicrobial functions of IL-17A, IL-1β, and tumor necrosis factor-α are redundant such that all of these cytokines can induce expression of neutrophil chemoattractants in epithelial cells (Godinez et al., 2011). It is more likely that broadly compromised host defenses are a result of immunodeficiencies further upstream that affect multiple inflammatory and immune response pathways.

Predictably, data suggest that deficiencies in cytokines and receptors further downstream in the IL-23/Th17 pathway are associated with fewer disorders than deficiencies in upstream components of the pathway. For example, dysregulation of IL12RB1, which encodes a common subunit of the IL-12 and IL-23 receptor, is associated with increased susceptibility to a range of infections, including MSMD, Salmonella, and tuberculosis, whereas the potential consequences of more downstream IL-17 deficiencies are generally limited to superficial skin and mucosal fungal infections. Observations are consistent with the involvement of upstream cytokines in pleotropic processes, including the regulation of other cytokines, whereas downstream cytokines are generally effectors of specific target tissue responses. Deficiencies in signaling pathways used by several cytokines also tend to be associated with a higher number of associated disorders. As shown in Figure 1b, upstream cytokines are more broadly involved in defense mechanisms against a range of bacterial, fungal, and opportunistic infections compared with downstream cytokines (Bustamante et al., 2008; Di Cesare et al., 2009; Furst, 2010; Chu, 2013). In contrast, human deficiencies in receptors for downstream cytokines, most notably in the IL-17 family (IL-17A through F), tend to manifest as increased susceptibility to a fewer specific types of infection, including mucocutaneous candidiasis and cutaneous Staphylococcal infections alone (Gaffen, 2011; Cypowyj et al., 2012; Patel et al., 2013). The role of IL-17 cytokines in host defense against most other common pathogens is largely redundant; for example, both IL-17A and IL-17F are needed for mucocutaneous immunity against C. albicans (Girolomoni et al., 2012; van den Berg and Mclnnes, 2013), and no mutations in IL-17A resulting in generalized immunodeficiency have been identified to date (Cypowyj et al., 2012; Patel et al., 2013).

Overall, this paper has explored how patients inherently deficient in certain components of the IL-23/Th17 pathway may—and may not—be analogous to patients receiving agents that are also designed to target this pathway. Understanding the consequences of this inhibition may thus inform future long-term collection and analyses of data related to potential infectious complications of these agents.

CONFLICT OF INTEREST
Dr Blauvelt has served as a scientific consultant and clinical study investigator for AbbVie, Amgen, Boehringer Ingelheim, Celgene Corporation, Janssen Ortho Biotech, Eli Lilly & Co., Merck, Novartis, Pfizer, and Sandoz. Dr Lebwohl has served as a consultant or investigator for Abbott, Amgen, Anacor Pharmaceuticals, Inc., BioLineRX Ltd., Celgene Corporation, Coronado Biosciences, Dermispor, Eli Lilly & Co., Galderma, GlaxoSmithKline-Stiefel, Janssen Ortho Biotech, LEO Pharmaceuticals, Maruho Co., Ltd., Meda Pharmaceuticals, Novartis, Pfizer, Ranbaxy, and Valeant. Dr Bissonnette has served as a consultant, investigator, or speaker for, or received grants from, AbbVie, Amgen, Apopharma, Astellas, Celgene Corporation, Eli Lilly & Co., Galderma, GSK-Stiefel, Incyte, Janssen Ortho Biotech, Leo, Merck, Novartis, Pfizer, and Tribute.

ACKNOWLEDGMENTS
We thank Oxford PharmaGenesis Inc. for providing editorial assistance with editing and styling of the manuscript for submission. This assistance was funded by the Novartis Pharmaceuticals Corporation. The authors were fully responsible for all content and editorial decisions and received no financial support or other form of compensation related to the development of this manuscript.

REFERENCES

Akahoshi M, Nakashima H, Miyake K et al. (2003) Influence of interleukin-12 receptor β1 polymorphisms on tuberculosis. *Hum Genet* 112:237–43

Al-Muhsen S, Casanova JL. (2008) The genetic heterogeneity of Mendelian susceptibility to mycobacterial diseases. *J Allergy Clin Immunol* 122:1043–503

Altau F, Durandy A, Lammas D et al. (1998) Impairment of mycobacterial immunity in human interleukin-12 receptor deficiency. *Science* 280: 1432–5

Aujla SJ, Chan YR, Zheng M et al. (2008) IL-22 mediates mucosal host defense against Gram-negative bacterial pneumonia. *Nat Med* 14:275–81

Bedoya SK, Lam B, Lau K et al. (2013) Th17 cells in immunity and autoimmunity. *Clin Dev Immunol* 2013:986789

Blauvelt A (2008) T-helper 17 cells in psoriatic plaques and additional genetic links between IL-23 and psoriasis. *J Invest Dermatol* 128:1064–7

Boisson-Dupuis S, Kong XF, Okada S et al. (2012) Inborn errors of human STAT1: allelic heterogeneity governs the diversity of immunological and infectious phenotypes. *Curr Opin Immunol* 24:364–78

Bongartz T, Sutton AJ, Sweeting MJ et al. (2006) Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 295:2275–85

Bustamante J, Boisson-Dupuis S, Jouanguy E et al. (2008) Novel primary immunodeficiencies revealed by the investigation of paediatric infectious diseases. *Curr Opin Immunol* 20:39–48

Cárdenes M, Angel-Moreno A, Fieschi C et al. (2010) Oesophageal squamous cell carcinoma in a young adult with IL-12Rβ1 deficiency. *J Med Genet* 47: 635–7

Chu WM (2013) Tumor necrosis factor. *Cancer Lett* 328:222–5

Cypowyj S, Picard C, Marodi L et al. (2012) Immunity to infection in IL-17-deficient mice and humans. *Eur J Immunol* 42:2246–54

de Beaucouydey L, Samarena A, Bustamante J et al. (2010) Revisiting human IL-12Rβ1 deficiency—a survey of 141 patients from 30 countries. *Medicine (Baltimore)* 89:381–402
A Blauvelt et al.
Deficiency Phenotypes in the IL-23/Th17 Pathway

De Luca A, Zelante T, D’Angelo C et al. (2010) IL-22 defines a novel immune pathway of antifungal resistance. Mucosal Immunol 3:361–73

Di Cesare A, Di Meglio P, Nestle FO (2009) The IL-23/Th17 axis in the immunopathogenesis of psoriasis. J Invest Dermatol 129:1339–50

Drewniak A, Gazendam RP, Tool AT et al. (2013) Invasive fungal infection and impaired neutrophil killing in human CARD9 deficiency. Blood 121: 2385–92

Ferwerda B, Ferwerda G, Plantinga TS et al. (2009) Human dectin-1 deficiency and mucocutaneous fungal infections. N Engl J Med 361:1760–7

Fieschi C, Bosticardo M, de Beaucoudrey L et al. (2011) The IL-23 axis in Salmonella species clarify the basis of clinical phenotypes. Curr Opin Microbiol 14:1373–8

Fieschi C, Casanova JL (2003) The role of interleukin-12 in human infectious diseases: only a faint signature. Eur J Immunol 33:1461–4

Fieschi C, Casanova JL (2012) Unravelling fungal immunity through primary immune deficiencies. Curr Opin Microbiol 17: 1759–68

Furst DE (2010) The risk of infections with biologic therapies for rheumatoid arthritis. Semin Arthritis Rheum 39:327–46

Gaffen SL (2011) Recent advances in the IL-17 cytokine family. Curr Opin Immunol 23:613–9

Girolomoni G, Mrowietz U, Paul C (2012) Psoriasis: rationale for targeting interleukin-17. Br J Dermatol 167:217–24

Godinez I, Keestra AM, Spees A et al. (2011) The IL-23 axis in Salmomella gastroenteritis. Cell Microbiol 13:1639–47

Hanna S, Etzioni A (2011) New host defense mechanisms against Candida species clarify the basis of clinical phenotypes. J Allergy Clin Immunol 127: 1433–7

Harper EG, Guo C, Rizzo H et al. (2009) Th17 cytokines stimulate CCL20 expression in keratinocytes in vitro and in vivo: implications for psoriasis pathogenesis. J Invest Dermatol 129:2175–83

Hueber W, Patel DD, Dryja T et al. (2010) Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis. Sci Transl Med 2:52ra72

Huppler AR, Bishu S, Gaffen SL (2012) Mucocutaneous candidiasis: the IL-17 pathway and implications for targeted immunotherapy. Arthritis Res Ther 14:217

Kagami S, Rizzo HL, Lee J et al. (2010) Circulating Th17, Th22, and Th1 cells are increased in psoriasis. J Invest Dermatol 130:1373–83

Kellner H (2013) Targeting interleukin-17 in patients with active rheumatoid arthritis: rationale and clinical potential. Ther Adv Musculoskelet Dis 5: 141–52

Khader SA, Pearl JE, Sakamoto K et al. (2005) IL-23 compensates for the absence of IL-12p70 and is essential for the IL-17 response during tuberculosis but is dispensable for protection and antigen-specific IFN-γ responses if IL-12p70 is available. J Immunol 175:788–95

Kim SY, Solomon DH (2010) Tumor necrosis factor blockade and the risk of viral infection. Nat Rev Rheumatol 6:165–74

Kisand K, Roe Wolf AS, Podkrajsek KT et al. (2010) Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17-associated cytokines. J Exp Med 207:299–308

Kisand K, Lilic D, Casanova JL et al. (2011) Mucocutaneous candidiasis and autoimmunity against cytokines in APECED and thymoma patients: clinical and pathogenetic implications. Eur J Immunol 41:1517–27

Kluger N, Ranki A, Krohn K (2012) APECED: this is a model for failure of T cell and B cell tolerance! Front Immunol 3:232

Leombruno JP, Einarton TR, Keystone EC (2009) The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. Ann Rheum Dis 68: 1136–45

Lilic D (2012) Uncavelling fungal immunity through primary immune deficiencies. Curr Opin Microbiol 15:420–6

Liu L, Okada S, Kong XF et al. (2011) Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. J Exp Med 208:1635–48

Lynde CW, Poulin Y, Vender R et al. (2014) Interleukin 17A: Toward a new understanding of psoriasis pathogenesis. J Am Acad Dermatol 71: 141–50

Ma CS, Chew GY, Simpson N et al. (2008) Deficiency of Th17 cells in hyper IgE syndrome due to mutations in STAT3. J Exp Med 205:1551–7

MacLennan C, Fieschi C, Lammas DA et al. (2004) Interleukin (IL)-12 and IL-23 are key cytokines for immunity against Salmonella in humans. J Infect Dis 190:1753–7

Malichak-Storna A, Pietrzyk A, Szepeiktowski JC et al. (2011) Cytokine network in psoriasis revisited. Eur Cytokine Netw 22:160–8

Minegishi Y, Karasuyama H (2009) Defects in Jak-STAT-mediated cytokine signals cause hyper-IgE syndrome: lessons from a primary immunodeficiency. Int Immunol 21:105–12

Nwe SM, Chapmain AH, Gordon KB (2013) Rationale and early clinical data on IL-17 blockade in psoriasis. Expert Rev Clin Immunol 9:677–82

O’Shea JJ, Ma A, Lipsky P (2002) Cytokines and autoimmunity. Nat Rev Immunol 2:37–45

Ortega C, Fernández-A S, Carrillo JM et al. (2009) IL-17-producing CD8+ T lymphocytes from psoriasis skin plaques are cytotoxic effector cells that secrete Th17-related cytokines. J Leukoc Biol 86:435–43

Ouederni M, Sanal O, Ikincigullari A et al. (2014) Clinical features of Candidiasis in patients with inherited interleukin 12 receptor β1 deficiency. Clin Infect Dis 58:204–13

Patel DD, Lee DM, Kolbinger F et al. (2013) Effect of IL-17A blockade with secukinumab in autoimmune diseases. Ann Rheum Dis 72(Suppl 2): ii116–23

Puel A, Cypowyj S, Bustamante J et al. (2011) Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. Science 332:65–8

Puel A, Cypowyj S, Maródi L et al. (2012) Inborn errors of human IL-17 immunity underlie chronic mucocutaneous candidiasis. Curr Opin Allergy Clin Immunol 12:616–22

Puel A, Döffinger R, Natividad A et al. (2010a) Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I. J Exp Med 207:291–7

Puel A, Picard C, Cypowyj S et al. (2012b) Inborn errors of mucocutaneous immunity to Candida albicans in humans: a role for IL-17 cytokines? Curr Opin Immunol 22:467–74

Qu N, Xu M, Mizoguchi I et al. (2013) Pivotal roles of T-helper 17-related cytokines, IL-17, IL-22, and IL-23, in inflammatory diseases. Clin Dev Immunol 2013:968549

Rafatellu M, Santos RL, Verhoeven DE et al. (2008) Simian immunodeficiency virus-induced mucosal interleukin-17 deficiency promotes Salmonella dissemination from the gut. Nat Med 14:421–8

Ramirez-Alejo N, Blancas-Galicia L, Yamazaki-Nakashimada M et al. (2014) Molecular analysis for patients with IL-12 receptor β1 deficiency. Clin Genet 86:161–6

Res PC, Piskin G, de Boer OJ et al. (2010) Overrepresentation of IL-17A and IL-22 producing CD8 T cells in lesional skin suggests their involvement in the pathogenesis of psoriasis. PloS One 5:e14108

Rizzo HL, Kagami S, Phillipis KG et al. (2011) IL-23-mediated psoriasis-like epidermal hyperplasia is dependent on IL-17A. J Immunol 186: 1495–502

Schrinke LF, Sawalle-Belohradsky J, Roessler J et al. (2010) Diagnostic approach to the hyper-IgE syndromes: immunologic and clinical key findings to differentiate hyper-IgE syndromes from atopic dermatitis. J Allergy Clin Immunol 126:611–7.e1

Sillevs Smith JH, Kuipers TW (2013) Cutaneous manifestations of primary immunodeficiency. Curr Opin Pediatr 25:492–7

Szczerwańska-Popłonyk A, Kyeler Z, Pietrucha B et al. (2011) The hyperimmunoglobulin E syndrome—clinical manifestation diversity in primary immune deficiency. Orphanet J Rare Dis 6:76

1952 Journal of Investigative Dermatology (2015), Volume 135
Teixeira-Coelho M, Cruz A, Carmona J et al. (2011) TLR2 deficiency by compromising p19 (IL-23) expression limits T_{h} 17 cell responses to Mycobacterium tuberculosis. *Int Immunol* 23:89–96

Trinchieri G (1995) Interleukin-12: a proinflammatory cytokine with immunoregulatory functions that bridge innate resistance and antigen-specific adaptive immunity. *Annu Rev Immunol* 13:251–76

van de Veerdonk FL, Marijnissen RJ, Joosten LA et al. (2010) Milder clinical hyperimmunoglobulin E syndrome phenotype is associated with partial interleukin-17 deficiency. *Clin Exp Immunol* 159:57–64

van de Veerdonk FL, Plantinga TS, Hoischen A et al. (2011) STAT1 mutations in autosomal dominant chronic mucocutaneous candidiasis. *N Engl J Med* 365:54–61

van de Vosse E, Haverkamp MH, Ramirez-Alejo N et al. (2013) IL-12R{β}1 deficiency: mutation update and description of the IL12RB1 variation database. *Hum Mutat* 34:1329–39

van den Berg WB, McInnes IB (2013) Th17 cells and IL-17A—focus on immunopathogenesis and immunotherapeutics. *Semin Arthritis Rheum* 43:158–70

Waite JC, Skokos D (2012) Th17 response and inflammatory autoimmune diseases. *Int J Inflam* 2012:819467

Wang X, Wang W, Lin Z et al. (2014) CARD9 mutations linked to subcutaneous phaeohyphomycosis and T_{h}17 cell deficiencies. *J Allergy Clin Immunol* 133:905–8 e3

Yilmaz SB, Cicek N, Coskun M et al. (2012) Serum and tissue levels of IL-17 in different clinical subtypes of psoriasis. *Arch Dermatol Res* 304:465–9

Zelante T, De Luca A, D'Angelo C et al. (2009) IL-17/Th17 in anti-fungal immunity: what's new? *Eur J Immunol* 39:645–8

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by-nc-nd/4.0/