

REVIEW

Cytokines Focus

Targeting interleukin-17 in chronic inflammatory disease: A clinical perspective

Pascale Zwicky*¹, Susanne Unger*¹, and Burkhard Becher¹

Chronic inflammatory diseases like psoriasis, Crohn’s disease (CD), multiple sclerosis (MS), rheumatoid arthritis (RA), and others are increasingly recognized as disease entities, where dysregulated cytokines contribute substantially to tissue-specific inflammation. A dysregulation in the IL-23/IL-17 axis can lead to inflammation of barrier tissues, whereas its role in internal organ inflammation remains less clear. Here we discuss the most recent developments in targeting IL-17 for the treatment of chronic inflammation in preclinical models and in patients afflicted with chronic inflammatory diseases.

The IL-17 family

IL-17A, the founding member of the IL-17 family, was first discovered in mice in 1993 (Rouvier et al., 1993) and 2 yr later in humans (Yao et al., 1995b). The IL-17 family is evolutionary conserved within vertebrates and composes six structurally related members in mammals, IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F (Malagoli, 2016). All cytokines bind to their receptors as disulfide-linked homodimers, with the exception of IL-17A and IL-17F, which can also form heterodimers (Wright et al., 2007; Fig. 1).

Five IL-17 receptor subunits have been identified (IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE). All are single-pass transmembrane receptors with two extracellular fibronectin II-like domains and a cytoplasmatic “SEFIR” motif for activation of downstream signaling pathways (McGeachy et al., 2019). The receptor for IL-17A and IL-17F homodimers and IL-17A/F heterodimers consists of a heterodimeric receptor complex composed of IL-17RA and IL-17RC subunits. IL-17RA can also pair with IL-17RE or IL-17RB, which then bind IL-17C and IL-17E, respectively. IL-17B has been shown to engage with IL-17RB, but a coreceptor is still missing, as well as the cognate receptors for IL-17D and a cytokine that binds to IL-17RD.

IL-17R signal transduction has been best studied for IL-17RA/IL-17RC complexes after IL-17A ligation (Gu et al., 2013). Receptor engagement leads to a conformational change, which allows the adaptor protein Act1 to form a homotypic interaction between the receptor’s “SEFIR” domain and its own. The E3 ligase activity of Act1 initiates the canonical pathway via ubiquitylation of TNF receptor-associated factor 6 (TRAF6),

recruitment of TAK1 and subsequent activation of the canonical NF- κ B and MAPK pathways including ERK, p38, and JNK, as well as the CCAAT-enhancer-binding proteins pathway (Monin and Gaffen, 2018). An alternative pathway depends on the phosphorylation of Act1 by inducible I κ B kinase, which leads to the assembly of TRAF2 and TRAF5 with mRNA stabilizing factor human antigen R, thereby increasing stability of multiple mRNAs (Amatya et al., 2017). IL-17A and F lie in close proximity in the genome on chromosome 1 in mice and chromosome 6 in humans, share the highest structural identity among all IL-17 family members, and have been shown to have largely overlapping biological activities (Akimzhanov et al., 2007; Monin and Gaffen, 2018). Hereafter, we focus on IL-17A/F and their role in chronic inflammatory disorders and use IL-17 as shorthand.

T helper (Th) 17 cell polarization and other sources of IL-17

Mosmann et al. (1986) were the first to propose a bifurcation in CD4⁺ Th cells. Th1 cells were defined as mediators of “cellular immunity” directed against intracellular pathogens and were characterized mainly by their production of IL-2 and IFN- γ , but also other cytokines such as GM-CSF and TNF. Th2 cells were described as IL-4, IL-5, IL-13, and IL-10-secreting cells involved in “humoral immunity” directed against extracellular pathogens (reviewed in Raphael et al., 2015). The discovery of IL-17 initially did not influence the Th1/Th2 paradigm prevailing in the field at this time even though numerous reports indicated that it could be involved in several inflammatory disorders (Kotake et al., 1999; Kostulas et al., 1999; Antonysamy et al., 1999; Chabaud

.....
 Institute of Experimental Immunology, Department of Inflammation Research, University of Zurich, Zurich, Switzerland.

*P. Zwicky and S. Unger contributed equally to this paper; Correspondence to Burkhard Becher: becher@immunology.uzh.ch.

© 2019 Zwicky et al. This article is distributed under the terms of an Attribution–Noncommercial–Share Alike–No Mirror Sites license for the first six months after the publication date (see <http://www.rupress.org/terms/>). After six months it is available under a Creative Commons License (Attribution–Noncommercial–Share Alike 4.0 International license, as described at <https://creativecommons.org/licenses/by-nc-sa/4.0/>).

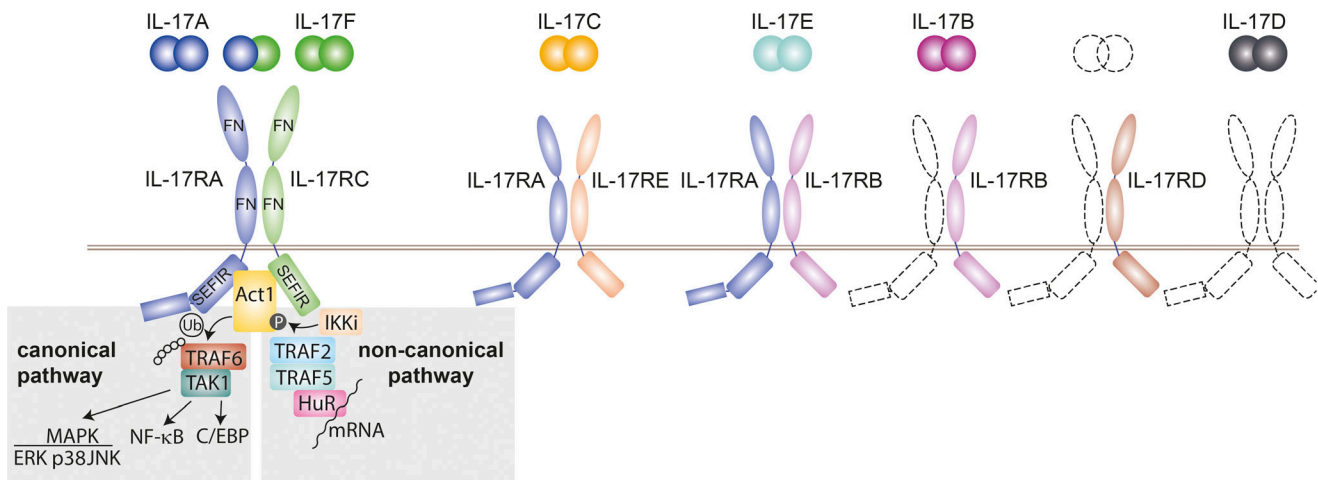


Figure 1. **IL-17 cytokine and receptor family.** Schematic overview of the known heterodimeric IL-17 receptor complexes with their respective IL-17 cytokines. Unknown coreceptors and ligands are displayed with dashed lines. IL-17 receptors share a common structure with two extracellular fibronectin II-like (FN) domains and an intracellular SEFIR domain. Downstream signaling events depend on the adaptor Act1. In the canonical pathway Act1 ubiquitinates TRAF6, leading to recruitment of TAK1 and triggering of NF-κB, MAPK pathways, and the CCAAT-enhancer-binding proteins (C/EBP) pathway. The noncanonical pathway is initiated by phosphorylation of Act1 by inducible IκB kinase (IKKi) and the subsequent formation of a complex with TRAF2, TRAF5, and mRNA stabilizing factor human antigen R (HuR), which increases the half-life of several mRNAs. Ub, ubiquitin; P, phosphoryl group.

et al., 1998, 1999). Langrish et al. (2005) found that among many other mediators, IL-17A is produced by Th cells upon engagement of their IL-23R. In vitro, IL-17 secretion could be elicited from naive CD4 T cells upon polarization with TGF-β and IL-6 (Veldhoen et al., 2006). In humans, IL-6 and IL-1β and IL-21 were later also identified as promoters of the IL-17 expression in Th cells (reviewed in Sallusto et al., 2012). IL-17 expression is driven by the transcription factor RORγt (via a STAT3-dependent mechanism; Ivanov et al., 2006). The term Th17 cell was coined, and for some time Th17 polarization and their role in immunity became the core interest of the immunology community. The discovery and characterization of Th17 cells are reviewed in more detail elsewhere (Korn et al., 2009; McGeachy and Cua, 2008). Over the years, it crystallized that the commonly called “IL-23/IL-17 axis” is critically involved in the regulation of tissue inflammation, in the context of both host defense and chronic inflammatory disorders.

In addition to Th17 cells, innate cells located at epithelial and mucosal barriers such as CD27⁺ γδ T cells, NK(T) cells, and innate lymphoid cells (ILCs) emerged as potent IL-17 producers (Happel et al., 2003; Ferretti et al., 2003; Zheng et al., 2008; Fig. 2). Their constitutive IL-23R and RORγt expression allows them to respond quickly (within hours) to injury or pathogenic triggers (reviewed in Cua and Tato, 2010). Also, other leukocytes such as CD8 T cells and B cells and even Paneth cells have been reported as cellular sources of IL-17 (He et al., 2006; Schlegel et al., 2013; Vazquez-Tello et al., 2012; Takahashi et al., 2008; Fig. 2). Whether myeloid cells such as neutrophils or macrophages produce IL-17 is still controversially discussed (see Fig. 2).

IL-17 is a pleiotropic cytokine that acts mainly on cells of mesenchymal origin such as endothelial cells, epithelial cells, and fibroblasts but has also effects on immune cells including dendritic cells and macrophages (reviewed in Xu and Cao, 2010;

Fig. 2). IL-17 executes key functions to prevent pathogen invasion by the secretion of proinflammatory cytokines, chemokines, matrix metalloproteinases, growth factors, and antimicrobial peptides (reviewed in Onishi and Gaffen, 2010). Hereby IL-17 often acts in synergy with other mediators such as TNF and IL-22 (Shen et al., 2005; Albanesi et al., 1999). Conversely, excessive IL-17 production contributes via similar mechanisms to pathogenic inflammation.

IL-17 in chronic inflammation

Most of our understanding of IL-17 and its role in inflammatory disorders was gained through various preclinical models of disease and has prompted the development of new drugs targeting IL-17. Several drugs were designed to block the IL-17 pathway either selectively or in combination with other inflammatory cytokines, or cytokines involved in the maintenance of IL-17 producing cells such as IL-23. Table 1 summarizes the therapeutic agents that are already approved or in clinical development. In the following section, we will discuss preclinical experimental findings about the role of IL-17 in prototypic chronic inflammatory disorders and compare the results to data from clinical trials.

Targeting IL-17 in inflammatory disorders affecting skin and mucosal barriers

Psoriasis

Psoriasis is a chronic immune-mediated skin disease, characterized by the proliferation of keratinocytes and infiltration of T cells (Nikaein et al., 1991). In xenograft models of psoriasis, nonlesional skin from psoriasis patients is transplanted onto immunocompromised mice (Boehncke et al., 1994; Boyman et al., 2004). The model uncovered a pathogenic role of IL-23 (Tonel et al., 2010), IFN-α (Nestle et al., 2005), and TNF (Boyman et al., 2004) in psoriasis and paved the path for the successful

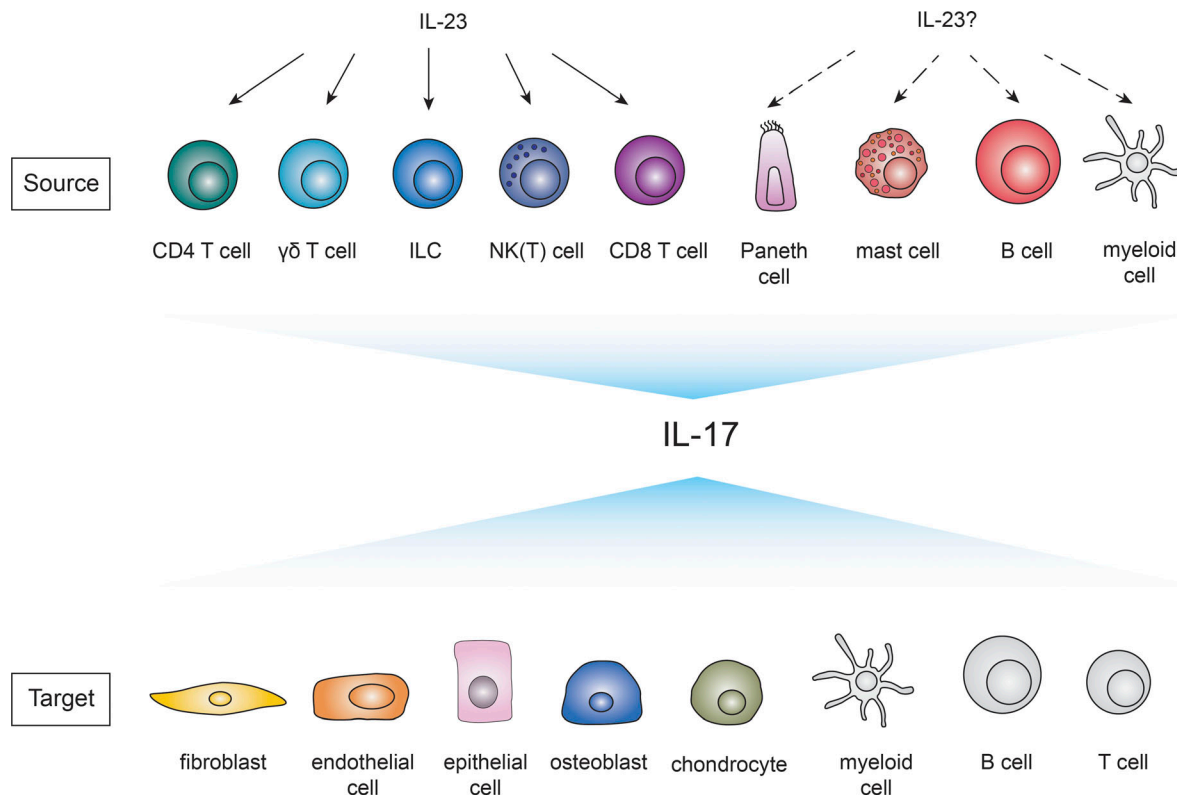


Figure 2. Cellular sources and targets of IL-17A/F. Overview of described cellular sources (top row) and targets (bottom row) of IL-17A/F. IL-23 induces IL-17 production in CD4 T cells (Aggarwal et al., 2003), $\gamma\delta$ T cells (Sutton et al., 2009), NK(T) cells (Michel et al., 2007; Passos et al., 2010), ILCs (Buonocore et al., 2010), and CD8 T cells (Happel et al., 2003). The dependence of IL-23 on other IL-17-producing cells as Paneth cells (Takahashi et al., 2008), mast cells (Lin et al., 2011; Mashiko et al., 2015), and B cells (Schlegel et al., 2013) has to be determined. Whether myeloid cells (depicted in gray) produce IL-17 is still controversially discussed (Ferretti et al., 2003; Song et al., 2008; Li et al., 2010; Tamassia et al., 2018). IL-17RA is ubiquitously expressed, but the main targets of IL-17 include endothelial cells, epithelial cells, fibroblasts (Fossiez et al., 1996), osteoblasts (Kotake et al., 1999), and chondrocytes (Shalom-Barak et al., 1998). Less-studied potential cellular targets of IL-17 (depicted in gray) are myeloid cells and B and T cells.

introduction of TNF inhibitors as therapeutic options for psoriasis vulgaris (Leonardi et al., 2003). In 2009, van der Fits et al. (2009) introduced the Aldara (5% Imiquimod)-model of psoriasis, which very closely mimics human psoriasiform lesions. We and others then found that psoriasiform inflammation greatly depends on the IL-23/IL-17 axis (Pantelyushin et al., 2012; Cai et al., 2011). Skin of Aldara-treated mice expressed high levels of IL-17A/F (Pantelyushin et al., 2012; Cai et al., 2011) and IL-22 (Pantelyushin et al., 2012). In line with this, it was reported that IL-17A, IL-22, and IL-23 are up-regulated in the serum of patients with active psoriasis, and increased levels of IL-17A, F, and C were found in psoriatic skin lesions (Johansen et al., 2009; Fotiadou et al., 2015). Surprisingly, $\gamma\delta$ T cells and not Th17 cells were found to be the primary source of IL-17A/F in the Aldara-mouse model, and their ablation led to disease protection (Cai et al., 2011; Pantelyushin et al., 2012). Similarly, increased numbers of IL-17 producing $\gamma\delta$ T cells were also found in the skin of psoriasis patients (Laggner et al., 2011). There is some debate as to which cells in developing lesions initially deliver IL-17 as CD8⁺ IL-17 producing cells were also identified in psoriatic lesions (Ortega et al., 2009). The disease-promoting role of IL-17 in psoriasiform inflammation was shown to be mainly mediated via the activation of epithelial cells and keratinocytes and their increased secretion of antimicrobial peptides, cytokines, and

chemokines mobilizing the recruitment of neutrophils (reviewed in Perera et al., 2012).

After the identification of the IL-23/IL-17 axis as a key factor in the pathogenesis of psoriasis, Ustekinumab, the first p40 inhibitor targeting both IL-12 and IL-23, was introduced to the clinic with success (Papp et al., 2008). However, we found that only IL-23 is disease-promoting in psoriasiform inflammation, whereas IL-12 has a protective role (Kulig et al., 2016), suggesting that collateral neutralization of IL-12 instead of IL-23 alone limited the effectiveness of these drugs.

Recently, the first three selective IL-23 inhibitors targeting the IL-23p19 subunit were licensed for treatment of plaque psoriasis after successful completion of several phase III clinical trials: Tildrakizumab, Risankizumab, and Guselkumab (Reich et al., 2017; Gordon et al., 2018; Blauvelt et al., 2017b). IL-23p19 inhibitors were more efficient in improving skin lesions than TNF inhibitors (Reich et al., 2017) and in line with findings from the Aldara-model of psoriasiform inflammation, superior compared with IL-12/IL-23 inhibitor Ustekinumab (Gordon et al., 2018). The selective IL-23 inhibitor Guselkumab was also effective in psoriasis patients where combined IL-12/IL-23 inhibition had failed (Langley et al., 2018), emphasizing that sparing IL-12 is necessary for resolution of skin inflammation in some psoriasis patients.

Table 1. Clinical development of IL-17/IL-23 inhibitors in chronic inflammatory diseases

Target	Drug and trade names	Barrier tissues			Nonbarrier tissues				
		Plaque psoriasis	IBD	Other diseases	PsA	Ankylosing spondylitis	RA	MS	Other diseases
IL-17A	Secukinumab (AIN457; Cosentyx)	Approved	Phase II, terminated (ineffective); NCT01009281 (Hueber et al., 2012)	Asthma: Phase II, terminated (ineffective); NCT01478360 Atopic dermatitis: Phase II; NCT02594098 Hidradenitis suppurativa: Phase II; NCT03713632 Pityriasis rubra pilaris: Phase I; NCT03342573	Approved	Approved	Phase III, terminated; NCT01377012	Phase II, terminated; NCT01051817 (Havrdová et al., 2016)	Diabetes mellitus type 1: Phase II, terminated (business reasons); NCT02044848 Giant cell arteritis: Phase II; NCT03765788
IL-17A	Ixekizumab (Taltz)	Approved			Approved	Phase III; NCT02696785 (van der Heijde et al., 2018)	Phase II; NCT00966875 (Genovese et al., 2014)		
IL-17A	Netakimab (BCD-085)	Phase III; NCT03390101			Phase III; NCT03598751	Phase III; NCT03447704			Primary biliary cirrhosis: Phase II; NCT03476993
IL-17A	CNTO 6785						Phase II (ineffective); NCT01909427 (Mease et al., 2018b)		
IL-17A	CJM112	Phase I, terminated; NCT01828086		Asthma: Phase II; NCT03299686 Hidradenitis suppurativa: Phase II; NCT02421172					
IL-17A / IL-17F	Bimekizumab	Phase III; NCT03598790		Hidradenitis suppurativa: Phase II; NCT03248531	Phase III; NCT03896581; NCT03895203	Phase III; NCT03928743			
IL-17A/ IL-17F	M1095 (ALX-0761)	Phase II NCT03384745							
IL-17RA	Brodalumab (Siliq; Kyntheum)	Approved	Phase II, terminated (disease worsening); NCT00966875 (Targan et al., 2016)	Asthma: Phase II, terminated (ineffective); NCT01902290 Phase II (ineffective); NCT01199289 (Busse et al., 2013)	Phase III, terminated (sponsor decision); NCT02029495 (Mease et al., 2014)	Phase II, withdrawn (sponsor decision); NCT02429882	Phase II, terminated (ineffective); NCT00950989 (Pavelka et al., 2015)		

Table 1. Clinical development of IL-17/IL-23 inhibitors in chronic inflammatory diseases (Continued)

Target	Drug and trade names	Barrier tissues			Nonbarrier tissues				
		Plaque psoriasis	IBD	Other diseases	PsA	Ankylosing spondylitis	RA	MS	Other diseases
IL-17A/ TNF	ABT-122				Phase II, (ineffective); NCT02349451 (Mease et al., 2018a)			Phase II, (ineffective); NCT02433340, NCT02349451 (Khatri et al., 2019)	
IL-17A/ TNF	COVA 322	Phase II, terminated (safety profile); NCT02243787							
IL-17/IL- 6	MT-6194								Preclinical (Lyman et al., 2018)
IL-17/ BAFF	LY3090106							Phase I; NCT01925157	Sjögren's syndrome: Phase I; NCT02614716
IL-23p19	Risankizumab (Skyrizi)	Approved	Crohn's disease: Phase III; NCT03104413, NCT03105102, NCT03105128	Asthma: Phase II; NCT02443298	Phase III; NCT03675308, NCT03671148	Phase II (ineffective); NCT02047110 (Baeten et al., 2018)			
			Ulcerative colitis: Phase III; NCT03398148, NCT03398135	Atopic dermatitis: Phase II; NCT03706040					
				Hidradenitis suppurativa: Phase II; NCT03926169					
IL-23p19	Tildrakizumab (Ilumetri; Ilumya)	Approved			Phase II; NCT03552276, NCT02980692	Phase III; NCT03552276			
IL-23p19	Guselkumab (Tremfya)	Approved	Crohn's disease: Phase III; NCT03466411		Phase III; NCT03796858, NCT03158285, NCT03162796		Phase II (ineffective); NCT01645280 (Smolen et al., 2017)		
IL-23p19	Brazikumab (AMG 139)	Phase I; NCT01094093	Crohn's disease: Phase III; NCT03961815, NCT03759288						
			Ulcerative colitis: Phase II; NCT03616821						
IL-23p19	Mirikizumab (LY 3074828)	Phase III; NCT03535194	Crohn's disease: Phase III; NCT03926130						
			Ulcerative colitis: Phase II; NCT03524092						

Source: <https://clinicaltrials.gov> if not otherwise specified. NCT, Clinicaltrials.gov identifier.

Between 2015 and 2017, three IL-17 pathway inhibitors reached the market. Secukinumab and Ixekizumab are monoclonal antibodies specific for IL-17A and thus inhibit both IL-17A homodimers as well as IL-17A/F heterodimers (Liu et al., 2016), while IL-17F homodimers remain unaffected. In contrast, the monoclonal antibody Brodalumab targets IL-17RA, and thus blocks the activity of IL-17A, IL-17F, IL-17C, and IL-17E. All three biologicals are approved by the Food and Drug Administration and European Medicine Agency for the treatment of moderate to severe plaque psoriasis. Several pivotal phase III studies demonstrated rapid and sustained skin improvement in the treated patients compared with placebo (Langley et al., 2014; Gordon et al., 2016; Lebwohl et al., 2015). Depending on the design of the studies, up to 42% of patients who received one of the IL-17 pathway inhibitors achieved disease-free skin (Papp et al., 2016). Clinical responses are paralleled by decreased IL-17A, IL-17F, and IL-22 expression and downmodulation of leukocyte infiltration-promoting chemoattractants in the skin (Kolbinger et al., 2017).

IL-17 inhibitors showed superior efficacy in skin clearance than previously approved psoriasis therapy with IL-12/IL-23 inhibitor Ustekinumab (Blauvelt et al., 2017c; Paul et al., 2019; Lebwohl et al., 2015) or TNF inhibitor Etanercept (Griffiths et al., 2015; Langley et al., 2014). In addition, Ixekizumab demonstrated efficacy in Etanercept nonresponders (Blauvelt et al., 2017a) and Brodalumab in Ustekinumab nonresponders (Langley et al., 2014). Head-to-head trials comparing the efficacy between the available IL-17 and IL-23p19 inhibitors have not yet been performed, but a recent meta-analysis of 77 randomized controlled trials failed to detect a difference between the drug classes, as Brodalumab, Ixekizumab, Guselkumab, and Risankizumab were equally efficient to achieve skin improvement (Sawyer et al., 2019).

Besides its presence in diseased skin, IL-17 is also observed in healthy skin and has a nonredundant role in tissue protection and immunity against fungi (Naik et al., 2015, 2017; Linehan et al., 2018; Okada et al., 2016; Sparber et al., 2019). In spite of this, the safety profile of IL-17 pathway inhibitors is favorable over long-term treatment with a consistent spectrum of adverse events across all three therapies (Deodhar et al., 2019; Langley et al., 2019; Lebwohl et al., 2015). Upper respiratory tract infections occur more frequently, followed by a higher susceptibility to mucocutaneous *Candida* spp. infections (Saunte et al., 2017).

We speculate that IL-17 production in cells associated with homeostasis in the skin is largely independent of IL-23R signaling, suggesting that the blockade of IL-23 would trigger fewer adverse effects compared with the general inhibition of IL-17, which may serve a function in homeostatic barrier maintenance and the control of the commensal flora. Indeed, the risk of *Candida* infections was lower when targeting IL-23p19 alone compared with studies with IL-17 inhibitors (Blauvelt et al., 2018). Whether IL-23 may be required for homeostatic IL-22 remains unclear.

Inflammatory bowel disease (IBD)

IBDs, which comprise of Crohn's disease and ulcerative colitis, are inflammatory conditions of the colon and small intestine

(Abraham and Cho, 2009). Single nucleotide polymorphisms in *IL23R* are associated with the susceptibility to IBD, and both increased IL-23 and IL-17 levels were found in colon biopsies of IBD patients, especially during active disease (Fujino et al., 2003; Duerr et al., 2006; Hölttä et al., 2008).

Also in mouse models of IBD, IL-23 was clearly associated with colitis, and as for psoriasis and experimental autoimmune encephalomyelitis (EAE), an animal model for multiple sclerosis (MS), IL-23 and not IL-12 is critically driving the disease (Buonocore et al., 2010; Ahern et al., 2010; Yen et al., 2006; Hue et al., 2006; Elson et al., 2007). In contrast, targeting IL-17 or its receptors led to controversial results in different animal models of colitis. Already in 2004, Ogawa et al. (2004) showed that neutralization of IL-17 leads to increased disease severity in the dextrane sulfate sodium (DSS) model. Several studies confirmed this result in the DSS as well as in other models of IBD (O'Connor et al., 2009; Song et al., 2015; Lee et al., 2015; Maxwell et al., 2015) and are in conflict with the few reports showing a disease promoting role of IL-17 (Feng et al., 2011; Leppkes et al., 2009; Yen et al., 2006). Despite the description of a protective role of IL-17 in different murine models of colitis, IL-17A (Hueber et al., 2012) and IL-17RA inhibitors (Targan et al., 2016) were tested for therapeutic efficacy in patients with Crohn's disease. The treatment failed and the studies had to be terminated due to exacerbation of colitis. In fact, it was already proposed in the early 2000s that IL-17 has an important role in the maintenance of barrier properties of epithelial tissues in vitro and later also in vivo (Kinugasa et al., 2000; Lee et al., 2015). Two independent reports using different colitis models demonstrated that IL-17A increases the barrier integrity in epithelial cells and demonstrated that tissue-protective IL-17 is produced by $\gamma\delta$ T cells in the absence of IL-23 (even though they do express IL-23R; Lee et al., 2015; Maxwell et al., 2015).

Interestingly, new-onset IBD is a rare adverse event in psoriasis patients treated with IL-17 inhibitors (Schreiber et al., 2019), and mucosal inflammation is also not part of the disease spectrum in patients with inborn errors of the IL-17 pathway (Okada et al., 2016). However, during an established mucosal inflammation like in Crohn's disease, the beneficial function of IL-17 on the integrity of the epithelial barrier might prevail (Maxwell et al., 2015).

While IL-17 inhibition resulted in alarming disease exacerbation, IL-23 inhibition has revealed promising results in clinical trials for Crohn's disease (Feagan et al., 2017, 2018; Sands et al., 2017). These clinical data suggest that selective targeting of IL-23 allows the IL-23-independent IL-17 production in the gut needed to keep the epithelial barrier intact, while IL-23-driven disease-promoting IL-17-producing cells decrease, mirroring results from previous animal studies (Lee et al., 2015).

Given the critical role of IL-23 in the maintenance of disease-promoting IL-17-producing cells, selective IL-23 class inhibitors hold the promise to interfere especially with the development of these pathogenic IL-17-producing cells while sparing the IL-23-independent IL-17-producing cells involved in host defense against *Candida* and maintenance of the gut barrier. Several reports indicated that the protective effect of IL-17 could be

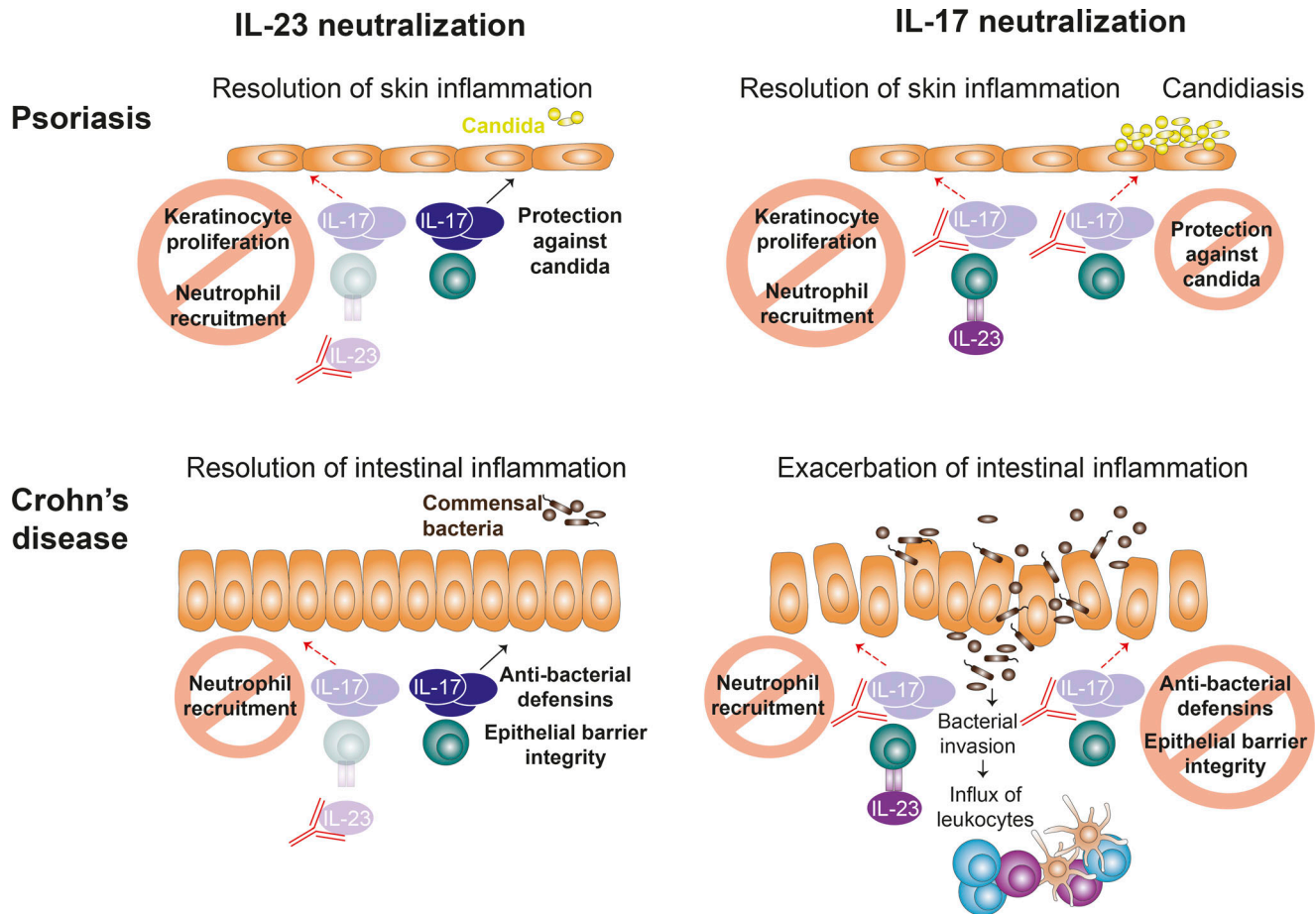


Figure 3. Effects of targeting IL-17 and IL-23 in psoriasis and Crohn's disease. The neutralization of IL-23 cures skin inflammation in psoriasis by interfering with the IL-23/IL-17 axis. Abrogation of pathogenic IL-23-dependent IL-17 production prevents IL-17-driven keratinocyte proliferation and neutrophil recruitment. IL-23-independent IL-17 production is preserved, which is needed for protection from *Candida* infections. Direct inhibition of IL-17 also reduces skin inflammation, but compromises host defense against *Candida*, leading to increased rates of candidiasis. Intestinal inflammation characteristic of Crohn's disease is improved upon IL-23 neutralization, which inhibits mainly IL-23-dependent IL-17 production and thus interferes with disease-driving mechanisms like neutrophil attraction. IL-23 neutralization spares IL-23-independent IL-17 production important for maintenance of epithelial barrier function and control of the commensal bacteria in the gut. In contrast, direct IL-17 inhibition exacerbates intestinal skin inflammation due to abrogation of the protective functions of IL-17 on epithelial integrity and microbiota control. This leads to invasion of luminal bacteria with a subsequent influx of immune cells and secretion of other pro-inflammatory cytokines to mount an immune response, which perpetuates intestinal inflammation.

mediated via the control of the commensal microflora (Tang et al., 2018; Song et al., 2015; Kumar et al., 2016), which were already earlier shown to induce IL-17 in the colon (Ivanov et al., 2009). Interestingly, disrupted IL-17R signaling in gut epithelial cells and the following dysbiosis was also connected to a higher predisposition to neuroinflammation, indicating that homeostatic IL-17R signaling in the gut is vital for a normal gut microflora, which in turn can control the auto-immune potential of lymphocytes (Kumar et al., 2016). Furthermore, it was shown that only deletion of IL-17F but not IL-17A prevents disease in both DSS and T cell-induced colitis models and that IL-17F promotes colitis by inhibiting the colonization of the gut by regulatory T cell-promoting commensals (Tang et al., 2018). These findings indicate that specific IL-17F inhibitors also could be a potential option for the treatment of Crohn's disease.

Fig. 3 summarizes the divergent roles of IL-23 and IL-17 inhibition in Crohn's disease and psoriasis.

Other chronic inflammatory disorders afflicting barrier tissues

The success of IL-17 inhibition in psoriasis encouraged the initiation of clinical trials in other chronic inflammatory diseases with elevated IL-17 expression. Serum IL-17 and IL-23 levels are increased in children with atopic dermatitis and correlated with disease severity (Leonardi et al., 2015). IL-17 and IL-23 inhibitors are currently in phase II trials; however, two trials with the combined IL-12/IL-23 inhibitor Ustekinumab failed to show superiority compared with placebo (Khattry et al., 2017; Saeki et al., 2017), suggesting redundancy of the IL-23/IL-17 axis in atopic dermatitis. Several case reports reported successful outcomes of patients suffering from Hidradenitis suppurativa (Jørgensen et al., 2018) and Pityriasis rubra pilaris (Wain et al., 2018) with IL-17 inhibitors, indicating shared pathomechanisms of these inflammatory skin diseases with psoriasis despite different clinical presentation. IL-17 pathway inhibition did not show a benefit over placebo for the treatment of asthma in multiple trials (Busse et al., 2013; see Table 1), suggesting that the

IL-23/IL-17 axis is not a major pathological driver in asthmatic airway inflammation.

Targeting IL-17 in inflammatory disorders affecting nonbarrier tissues

Overexpression of IL-17 in mice leads to inflammation of epithelial barriers as well as granulocytosis (Croxford et al., 2014; Haak et al., 2009). However, no inflammation-related symptoms of other, nonbarrier tissues are induced (Haak et al., 2009). This argues against the notion that the dysregulation of IL-17 would elicit immunopathology in nonbarrier tissues. The exception seems to be psoriasis arthritis (PsA), where inflammation of the skin usually precedes joint pathology and has a very different disease etiology than rheumatoid arthritis (RA). Nevertheless, the role of IL-17 in inflammatory disorders of nonbarrier tissues was extensively studied using preclinical models, and IL-17 inhibitors were tested in the clinics.

PsA

PsA is the most common psoriasis-associated disorder, found in up to 30% of psoriasis patients (Ritchlin et al., 2017; Villani et al., 2015) and is among others associated to polymorphisms in *IL23R* (Bowes et al., 2015). Increased numbers of IL-17 producing ILCs as well as CD4 and CD8 T cells are found in the synovial fluid of PsA patients (Benham et al., 2013; Leijten et al., 2015; Menon et al., 2014). In the joints, IL-17 seems to act on osteoblasts inducing osteoclast differentiation and thereby increases bone resorption (Sato et al., 2006). Until now, no specific murine model for has PsA existed. However, in some models for psoriasis, the development of arthritis was observed and demonstrated that changes in the skin can be sufficient to induce pathological changes in the joints (Zenz et al., 2005; Yamamoto et al., 2015; Croxford et al., 2014). In line with this, most drugs that are effective to treat psoriatic skin lesions also inhibit arthritis in PsA patients, indicating a shared pathophysiology (McInnes et al., 2013, 2015; Mease et al., 2015). However, it is still unclear how inflammatory processes in the skin, which often precede PsA, lead to arthritis (Eder et al., 2016).

Soon after the success in treating plaque psoriasis, Secukinumab and Ixekizumab received the Food and Drug Administration/European Medicine Agency approval for treatment of PsA (McInnes et al., 2015; Mease et al., 2017); Secukinumab has extended the approved indication spectrum even for ankylosing spondylitis (Baeten et al., 2015). Both IL-17A inhibitors have shown clinical efficacy and long-term improvements, even in patients unresponsive to first-line therapy with TNF inhibitors (Coates et al., 2018; Nash et al., 2017). However, compared with the high rates of complete skin clearance in plaque psoriasis, effects on PsA are relatively modest, possibly due to a less pronounced IL-17 signature in affected joints compared with skin (Belasco et al., 2015). The safety profile in the setting of both diseases is comparable to IL-17 pathway inhibition in plaque psoriasis (Mease et al., 2019; Deodhar et al., 2019).

IL-23 inhibition is effective in phase II clinical studies in PsA (Deodhar et al., 2018), and phase III studies are ongoing (NCT03552276), while there was no evidence of clinically meaningful improvements in ankylosing spondylitis (Baeten

et al., 2018), although both diseases respond well to IL-17 blockade. A hypothesis for the dichotomy of clinical efficacy is that in contrast to PsA, IL-17-producing cells become IL-23-independent in the chronic phase of joint inflammation in ankylosing spondylitis as shown in an animal model (van Tok et al., 2018). Counterintuitive to the proposed synergistic action of TNF and IL-17A in PsA, a recent study failed to show superiority of dual neutralization of TNF and IL-17A with a bi-specific antibody over TNF inhibition alone (Mease et al., 2018a).

RA

Early after the discovery of IL-17, several reports showed an association between IL-17 and RA, which is a systemic autoimmune disorder characterized by the chronic inflammation of several organs including the synovia of joints (Scott et al., 2010). Those reports demonstrated the presence of IL-17 and IL-17R in synovial fluids and tissue from RA patients, and synovial IL-17 expression was identified as being predictive for joint damage progression (Ziolkowska et al., 2000; Honorati et al., 2001; Kirkham et al., 2006; Chabaud et al., 1999, 1998). The main producers of IL-17 in synovial tissues of RA patients were identified as CD4⁺ memory T cells (Kotake et al., 1999). IL-17 was shown to potently induce cytokines such as TNF, IL-1 β , and GM-CSF from different joint cells as synovial fibroblasts, chondrocytes, and macrophages (Yao et al., 1995a, 1995b; Fossiez et al., 1996; Chabaud et al., 1998; Jovanovic et al., 1998) and was associated to bone and cartilage degradation (Chabaud et al., 2001; Cai et al., 2001; Chabaud and Miossec, 2001; Kim et al., 2015; Osta et al., 2015).

The disease-promoting role of IL-17 in RA was also described in mice. In wild-type mice, inflammatory arthritis can be induced by injecting recombinant IL-17 into the intra-articular space of knee joints (Chabaud et al., 2001; Cai et al., 2001). With rare exceptions (Doodes et al., 2008), the large majority of reports on IL-17 using different mouse models of RA showed that ablation of IL-17 reduced disease severity (Lubberts et al., 2001; Nakae et al., 2003; Katayama et al., 2013; Wu et al., 2010; Hirota et al., 2007; Duarte et al., 2010; Chabaud et al., 2001). The ablation of IL-17 was associated with reduced systemic levels of IL-6 as well as IL-1 β and RANKL (receptor activator of NF- κ B ligand)-producing cells in the synovium (Lubberts et al., 2004). Also, the transdifferentiation of Foxp3 regulatory T cells into IL-17-producing cells was associated to arthritis (Komatsu et al., 2014). Furthermore, it was proposed that changes in the microbiome and IL-17 in the gut are early events in RA (Wu et al., 2010), supporting the mucosal origins hypothesis suggesting that the disease-promoting immunity in RA is initiated at mucosal sites (leading to the circulation of auto-antibodies before clinical symptoms are observed) and only later spreads to the synovial joints generating symptomatic inflammation (reviewed in Holers et al., 2018).

Despite the extensive rationale from preclinical studies in mice and human to target IL-17 in RA, results from clinical studies fell far short of expectations. Although IL-17A inhibition was superior to placebo and improved symptoms in TNF non-responders (Blanco et al., 2017; Genovese et al., 2014), response rates were still lower compared with an established second-line

biological CTLA4-Ig, Abatacept (Blanco et al., 2017). As these studies provided evidence that IL-17A is a central pathogenic driver only in a small subgroup of RA patients and other available substance classes are more effective, clinical development was terminated after phase III (NCT01377012).

Many of the preclinical findings on IL-17 in RA were made using the collagen-induced arthritis (CIA) model where DBA-1 mice are immunized against type 2 collagen and immune response is boosted with CFA (Courtenay et al., 1980). Despite its valuable contributions to a better understanding of RA, in the CIA model, $\gamma\delta$ T cells are the main producers of IL-17, while these cells were hardly detected in joints of RA patients (Ito et al., 2009). We speculate that the CFA used in the CIA model induces the excessive IL-17 expression, thus inflating the role of IL-17 in the model compared with human RA.

Furthermore, it was recently shown that the transition of disease initiation to symptomatic arthritis could be mediated by IL-23 rather than IL-17. Pfeifle et al. (2017) found that IL-23-activated Th17 cells promoted the production of pro-inflammatory antibodies by B cells via IL-22 and IL-21, but not IL-17. However, at least in established RA, a recent study with a selective IL-23 inhibitor showed no improvement in disease symptoms (Smolen et al., 2017).

MS

As for other inflammatory disorders, dysregulated cytokines play an important role in MS. In 2002, it was shown that, as for psoriasis, IL-23 and not IL-12 is disease-promoting in the EAE model of MS (Cua et al., 2003; Becher et al., 2002). IL-23-deficient mice were shown to be resistant to EAE and had reduced levels of IL-17, while the transfer of IL-17-producing T cells led to disease exacerbation (Langrish et al., 2005). The presence of IL-17-producing cells in active brain lesions of MS patients (Tzartos et al., 2008) and increased IL-17 levels in cerebrospinal fluid especially during clinical exacerbation (Matusevicius et al., 1999), supported the idea that IL-17 might be implicated in MS pathogenesis.

Surprisingly, blockade of IL-17A or F in EAE only led to a disease reduction in SJL/J mice, but had only a modest effect in C57/BL6 mice (Park et al., 2005; Hofstetter et al., 2005; Komiyama et al., 2006; Langrish et al., 2005; Haak et al., 2009). McGeachy et al. (2007) reported that IL-17-producing Th cells are only pathogenic when they are driven by IL-23, but not by IL-6 and TGF β . In addition, IL-23 decreased the IL-10 expression by IL-17-producing cells, promoting their encephalitogenic capacity. In support of this, we found that IL-23 authorizes T cells to invade the central nervous system (CNS) and to polarize to Th17 cells (Gyölvézi et al., 2009). Furthermore, several reports suggested the existence of nonpathogenic Th17 cells (Yang et al., 2009; Esplugues et al., 2011). All these findings demonstrate that while IL-23 is essential for the development of EAE, IL-17 is largely redundant for disease development, and IL-23 seems to induce other pathogenic mediators. Indeed, we and others reported that IL-23 converts nonpathogenic into pathogenic T cells by the induction of GM-CSF (Codarri et al., 2011; El-Behi et al., 2011). Within the CNS of EAE mice, GM-CSF is produced almost exclusively by neuro-antigen-specific Th cells (Komuczki et al.,

2019), and systemic dysregulation of GM-CSF leads to severe and fatal CNS inflammation dominated by the invasion into the CNS of monocytes (Spath et al., 2017). Lee et al. (2012) found that T-bet, which was already associated to the expression of IL-23R in Th17 cells (Gocke et al., 2007) and protection from EAE (Panitch et al., 1987), is driving the pathogenic functions of Th17 cells independently of their IL-17 production (Lee et al., 2012). In line with this, clinically stable MS patients had higher expression of IL-10 in Th17 cells, and single-cell clones from patients with MS showed enhanced production of IL-17, GM-CSF, or IFN- γ , while in healthy controls, IL-10 dominated (Cao et al., 2015; Hu et al., 2017).

In summary, targeting of IL-17 does not efficiently inhibit disease formation in mice, whereas targeting IL-23 selectively blocks disease-promoting Th cells, independently of IL-17. The role of IL-17 in MS remains controversial. Although IL-17 pathway inhibition slowed down the formation of new Gd-enhancing T1 brain lesions in a phase II study, the trial was terminated because the cumulative number of lesions was not significantly different compared with placebo at the primary endpoint (Havrdová et al., 2016). Although according to preclinical data the new selective IL-23 inhibitors offer a promising strategy for MS, clinical trials have not been initiated yet. Combined IL-12/IL-23 inhibition failed to show clinical efficacy in patients (Segal et al., 2008; Vollmer et al., 2011), possibly by a negative effect of the concomitant IL-12 pathway inhibition.

Other nonbarrier-associated chronic inflammatory diseases

There are ongoing trials exploring the possibility of IL-17 inhibitors in primary biliary cirrhosis, giant cell arteritis, and Sjögren's syndrome (Table 1). The rationale for such trials came from observations that IL-17-producing cells were present in the inflammatory infiltrates of the respective affected organs of patients (Katt et al., 2013; Deng et al., 2010; Zhang et al., 2018). A clinical trial investigating IL-17 inhibition in diabetes mellitus type 1 patients was terminated during phase II (Table 1).

Concluding remarks

It is becoming increasingly clear that dysregulated cytokine networks are fundamentally involved in chronic inflammatory diseases and that targeting cytokines therapeutically has great value in treating patients suffering from these disorders. Of note, excessive production of single cytokines in transgenic mice actually led to tissue-specific inflammation (Keffer et al., 1991; Haak et al., 2009; Spath et al., 2017). IL-17 in particular is connected with barrier function, and dysregulation of IL-17 is closely linked to psoriasiform skin inflammation. The most likely explanation for the skin tropism of IL-17-mediated inflammation is the fact that the receptor complex for IL-17 is highly abundant in the skin compared with other tissues. The normal steady-state function is likely the control of the commensal microflora, and as a quasi-innate cytokine, IL-17 can rapidly recruit other leukocytes in response to dysbiosis or pathogen invasion through barriers. So, neutralization of the IL-17/IL-23 axis has been shown to be beneficial in treating psoriasis, while in Crohn's disease only the targeting of IL-23 shows clinical benefit, possible because the steady-state function of

IL-17 in gut barrier function is too fragile for external intervention. Nevertheless, the impact of the IL-23/IL-17 axis on the microbiome is abundantly clear. The nature of the commensal flora in the steady-state has in turn a dramatic effect on immunity in general. We thus propose that the conflicting data regarding the role of IL-17 in preclinical models of inflammation (outside of barrier tissues) is likely the result of the altered gut immune axis observed in IL-17-deficient mice. The clinical success of targeting the IL-17/IL-23 axis in chronic inflammation of the body lining but not of diseases of internal organs (e.g., RA, diabetes mellitus type 1, MS, etc.), was largely predicted in the preclinical studies, which provides further support for integrative and comprehensive bench to bedside research.

Acknowledgments

This work was supported by grants from the Swiss National Science Foundation (310030_146130, 316030_150768, and 310030_170320 to B. Becher), the European Union FP7 Project ATECT (Advanced T-cell Engineered for Cancer Therapy; to B. Becher), the European Union H2020 Project iPC (Individualized Paediatric Cure), and the University Research Priority Project Translational Cancer Research (to B. Becher).

The authors declare no competing financial interests.

Author contributions: S. Unger, P. Zwicky, and B. Becher wrote the manuscript.

Submitted: 19 June 2019

Revised: 26 August 2019

Accepted: 8 October 2019

References

- Abraham, C., and J.H. Cho. 2009. Inflammatory bowel disease. *N. Engl. J. Med.* 361:2066–2078. <https://doi.org/10.1056/NEJMra0804647>
- Aggarwal, S., N. Ghilardi, M.H. Xie, F.J. de Sauvage, and A.L. Gurney. 2003. Interleukin-23 promotes a distinct CD4 T cell activation state characterized by the production of interleukin-17. *J. Biol. Chem.* 278:1910–1914. <https://doi.org/10.1074/jbc.M207577200>
- Ahern, P.P., C. Schiering, S. Buonocore, M.J. McGeachy, D.J. Cua, K.J. Maloy, and F. Powrie. 2010. Interleukin-23 drives intestinal inflammation through direct activity on T cells. *Immunity.* 33:279–288. <https://doi.org/10.1016/j.immuni.2010.08.010>
- Akimzhanov, A.M., X.O. Yang, and C. Dong. 2007. Chromatin remodeling of interleukin-17 (IL-17)-IL-17F cytokine gene locus during inflammatory helper T cell differentiation. *J. Biol. Chem.* 282:5969–5972. <https://doi.org/10.1074/jbc.C600322200>
- Albanesi, C., A. Cavani, and G. Girolomoni. 1999. IL-17 is produced by nickel-specific T lymphocytes and regulates ICAM-1 expression and chemokine production in human keratinocytes: synergistic or antagonist effects with IFN-gamma and TNF-alpha. *J. Immunol.* 162:494–502.
- Amatya, N., A.V. Garg, and S.L. Gaffen. 2017. IL-17 Signaling: The Yin and the Yang. *Trends Immunol.* 38:310–322. <https://doi.org/10.1016/j.it.2017.01.006>
- Antonymsamy, M.A., W.C. Fanslow, F. Fu, W. Li, S. Qian, A.B. Troutt, and A.W. Thomson. 1999. Evidence for a role of IL-17 in organ allograft rejection: IL-17 promotes the functional differentiation of dendritic cell progenitors. *J. Immunol.* 162:577–584.
- Baeten, D., J. Sieper, J. Braun, X. Baraliakos, M. Dougados, P. Emery, A. Deodhar, B. Porter, R. Martin, M. Andersson, et al. MEASURE 2 Study Group. 2015. Secukinumab, an Interleukin-17A Inhibitor, in Ankylosing Spondylitis. *N. Engl. J. Med.* 373:2534–2548. <https://doi.org/10.1056/NEJMoa1505066>
- Baeten, D., M. Østergaard, J.C.-C. Wei, J. Sieper, P. Järvinen, L.-S. Tam, C. Salvarani, T.-H. Kim, A. Solinger, Y. Datsenko, et al. 2018. Risankizumab, an IL-23 inhibitor, for ankylosing spondylitis: results of a randomised, double-blind, placebo-controlled, proof-of-concept, dose-finding phase 2 study. *Ann. Rheum. Dis.* 77:1295–1302. <https://doi.org/10.1136/annrheumdis-2018-213328>
- Becher, B., B.G. Durell, and R.J. Noelle. 2002. Experimental autoimmune encephalitis and inflammation in the absence of interleukin-12. *J. Clin. Invest.* 110:493–497. <https://doi.org/10.1172/JCI0215751>
- Belasco, J., J.S. Louie, N. Gulati, N. Wei, K. Nograla, J. Fuentes-Duculan, H. Mitsui, M. Suárez-Fariñas, and J.G. Krueger. 2015. Comparative genomic profiling of synovium versus skin lesions in psoriatic arthritis. *Arthritis Rheumatol.* 67:934–944. <https://doi.org/10.1002/art.38995>
- Benham, H., P. Norris, J. Goodall, M.D. Wechalekar, O. FitzGerald, A. Szentpetery, M. Smith, R. Thomas, and H. Gaston. 2013. Th17 and Th22 cells in psoriatic arthritis and psoriasis. *Arthritis Res. Ther.* 15:R136. <https://doi.org/10.1186/ar4317>
- Blanco, F.J., R. Möricke, E. Dokoupilova, C. Codding, J. Neal, M. Andersson, S. Rohrer, and H. Richards. 2017. Secukinumab in Active Rheumatoid Arthritis: A Phase III Randomized, Double-Blind, Active Comparator- and Placebo-Controlled Study. *Arthritis Rheumatol.* 69:1144–1153. <https://doi.org/10.1002/art.40070>
- Blauvelt, A., K.A. Papp, C.E.M. Griffiths, L. Puig, J. Weisman, Y. Dutronc, L.F. Kerr, D. Ilo, L. Mallbris, and M. Augustin. 2017a. Efficacy and Safety of Switching to Ixekizumab in Etanercept Non-Responders: A Subanalysis from Two Phase III Randomized Clinical Trials in Moderate-to-Severe Plaque Psoriasis (UNCOVER-2 and -3). *Am. J. Clin. Dermatol.* 18:273–280. <https://doi.org/10.1007/s40257-016-0246-9>
- Blauvelt, A., K.A. Papp, C.E.M. Griffiths, B. Randazzo, Y. Wasfi, Y.-K. Shen, S. Li, and A.B. Kimball. 2017b. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *J. Am. Acad. Dermatol.* 76:405–417. <https://doi.org/10.1016/j.jaad.2016.11.041>
- Blauvelt, A., K. Reich, T.-F. Tsai, S. Tyring, F. Vanaclocha, K. Kingo, M. Ziv, A. Pinter, R. Vender, S. Hugot, et al. 2017c. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: Results from the CLEAR study. *J. Am. Acad. Dermatol.* 76:60–69.e9. <https://doi.org/10.1016/j.jaad.2016.08.008>
- Blauvelt, A., K. Reich, K.A. Papp, A.B. Kimball, M. Gooderham, S.K. Tyring, R. Sinclair, D. Thaçi, Q. Li, N. Cichanowitz, et al. 2018. Safety of til-drakizumab for moderate-to-severe plaque psoriasis: pooled analysis of three randomized controlled trials. *Br. J. Dermatol.* 179:615–622. <https://doi.org/10.1111/bjd.16724>
- Boehncke, W.H., W. Sterry, A. Hainzl, W. Scheffold, and R. Kaufmann. 1994. Psoriasisform architecture of murine epidermis overlying human psoriatic dermis transplanted onto SCID mice. *Arch. Dermatol. Res.* 286:325–330. <https://doi.org/10.1007/BF00402223>
- Bowes, J., A. Budu-Aggrey, U. Huffmeier, S. Uebe, K. Steel, H.L. Hebert, C. Wallace, J. Massey, I.N. Bruce, J. Bluett, et al. 2015. Dense genotyping of immune-related susceptibility loci reveals new insights into the genetics of psoriatic arthritis. *Nat. Commun.* 6:6046. <https://doi.org/10.1038/ncomms7046>
- Boyman, O., H.P. Hefti, C. Conrad, B.J. Nickoloff, M. Suter, and F.O. Nestle. 2004. Spontaneous development of psoriasis in a new animal model shows an essential role for resident T cells and tumor necrosis factor- α . *J. Exp. Med.* 199:731–736. <https://doi.org/10.1084/jem.20031482>
- Buonocore, S., P.P. Ahern, H.H. Uhlrig, I.I. Ivanov, D.R. Littman, K.J. Maloy, and F. Powrie. 2010. Innate lymphoid cells drive interleukin-23-dependent innate intestinal pathology. *Nature.* 464:1371–1375. <https://doi.org/10.1038/nature08949>
- Busse, W.W., S. Holgate, E. Kerwin, Y. Chon, J. Feng, J. Lin, and S.-L. Lin. 2013. Randomized, double-blind, placebo-controlled study of brodalumab, a human anti-IL-17 receptor monoclonal antibody, in moderate to severe asthma. *Am. J. Respir. Crit. Care Med.* 188:1294–1302. <https://doi.org/10.1164/rccm.201212-2318OC>
- Cai, L., J.P. Yin, M.A. Starovasnik, D.A. Hogue, K.J. Hillan, J.S. Mort, and E.H. Filvaroff. 2001. Pathways by which interleukin 17 induces articular cartilage breakdown in vitro and in vivo. *Cytokine.* 16:10–21. <https://doi.org/10.1006/cyto.2001.0939>
- Cai, Y., X. Shen, C. Ding, C. Qi, K. Li, X. Li, V.R. Jala, H.G. Zhang, T. Wang, J. Zheng, and J. Yan. 2011. Pivotal role of dermal IL-17-producing $\gamma\delta$ T cells in skin inflammation. *Immunity.* 35:596–610. <https://doi.org/10.1016/j.immuni.2011.08.001>

- Cao, Y., B.A. Goods, K. Raddassi, G.T. Nepom, W.W. Kwok, J.C. Love, and D.A. Hafler. 2015. Functional inflammatory profiles distinguish myelin-reactive T cells from patients with multiple sclerosis. *Sci. Transl. Med.* 7:287ra74. <https://doi.org/10.1126/scitranslmed.aaa8038>
- Chabaud, M., and P. Miossec. 2001. The combination of tumor necrosis factor α blockade with interleukin-1 and interleukin-17 blockade is more effective for controlling synovial inflammation and bone resorption in an ex vivo model. *Arthritis Rheum.* 44:1293–1303. [https://doi.org/10.1002/1529-0131\(200106\)44:6<1293::AID-ART221>3.0.CO;2-T](https://doi.org/10.1002/1529-0131(200106)44:6<1293::AID-ART221>3.0.CO;2-T)
- Chabaud, M., F. Fossiez, J.L. Taupin, and P. Miossec. 1998. Enhancing effect of IL-17 on IL-1-induced IL-6 and leukemia inhibitory factor production by rheumatoid arthritis synoviocytes and its regulation by Th2 cytokines. *J. Immunol.* 161:409–414. <https://doi.org/10.4049/jimmunol.165.9.5332>
- Chabaud, M., J.M. Durand, N. Buchs, F. Fossiez, G. Page, L. Frappart, and P. Miossec. 1999. Human interleukin-17: A T cell-derived proinflammatory cytokine produced by the rheumatoid synovium. *Arthritis Rheum.* 42:963–970. [https://doi.org/10.1002/1529-0131\(199905\)42:5<963::AID-ANR15>3.0.CO;2-E](https://doi.org/10.1002/1529-0131(199905)42:5<963::AID-ANR15>3.0.CO;2-E)
- Chabaud, M., E. Lubberts, L. Joosten, W. van Den Berg, and P. Miossec. 2001. IL-17 derived from juxta-articular bone and synovium contributes to joint degradation in rheumatoid arthritis. *Arthritis Res.* 3:168–177. <https://doi.org/10.1186/ar294>
- Coates, L.C., D.D. Gladman, P. Nash, O. FitzGerald, A. Kavanaugh, T.K. Kvien, L. Gossec, V. Strand, L. Rasouliyan, L. Pricop, et al. FUTURE 2 study group. 2018. Secukinumab provides sustained PASDAS-defined remission in psoriatic arthritis and improves health-related quality of life in patients achieving remission: 2-year results from the phase III FUTURE 2 study. *Arthritis Res. Ther.* 20:272. <https://doi.org/10.1186/s13075-018-1773-y>
- Codarri, L., G. Gyölvésvi, V. Tosevski, L. Hesske, A. Fontana, L. Magnenat, T. Suter, and B. Becher. 2011. ROR γ t drives production of the cytokine GM-CSF in helper T cells, which is essential for the effector phase of autoimmune neuroinflammation. *Nat. Immunol.* 12:560–567. <https://doi.org/10.1038/ni.2027>
- Courtenay, J.S., M.J. Dallman, A.D. Dayan, A. Martin, and B. Mosedale. 1980. Immunisation against heterologous type II collagen induces arthritis in mice. *Nature.* 283:666–668. <https://doi.org/10.1038/283666a0>
- Croxford, A.L., S. Karbach, F.C. Kurschus, S. Wörtge, A. Nikolaev, N. Yogeve, S. Klebow, R. Schüler, S. Reissig, C. Piotrowski, et al. 2014. IL-6 regulates neutrophil microabscess formation in IL-17A-driven psoriasisform lesions. *J. Invest. Dermatol.* 134:728–735. <https://doi.org/10.1038/jid.2013.404>
- Cua, D.J., and C.M. Tato. 2010. Innate IL-17-producing cells: the sentinels of the immune system. *Nat. Rev. Immunol.* 10:479–489. <https://doi.org/10.1038/nri2800>
- Cua, D.J., J. Sherlock, Y. Chen, C.A. Murphy, B. Joyce, B. Seymour, L. Lucian, W. To, S. Kwan, T. Churakova, et al. 2003. Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. *Nature.* 421:744–748. <https://doi.org/10.1038/nature01355>
- Deng, J., B.R. Younge, R.A. Olshe, J.J. Goronzy, and C.M. Weyand. 2010. Th17 and Th1 T-cell responses in giant cell arteritis. *Circulation.* 121:906–915. <https://doi.org/10.1161/CIRCULATIONAHA.109.872903>
- Deodhar, A., A.B. Gottlieb, W.-H. Boehncke, B. Dong, Y. Wang, Y. Zhuang, W. Barchuk, X.L. Xu, and E.C. Hsia. CNTO1959PSA2001 Study Group. 2018. Efficacy and safety of guselkumab in patients with active psoriatic arthritis: a randomised, double-blind, placebo-controlled, phase 2 study. *Lancet.* 391:2213–2224. [https://doi.org/10.1016/S0140-6736\(18\)30952-8](https://doi.org/10.1016/S0140-6736(18)30952-8)
- Deodhar, A., P.J. Mease, I.B. McInnes, X. Baraliakos, K. Reich, A. Blauvelt, C. Leonardi, B. Porter, A. Das Gupta, A. Widmer, et al. 2019. Long-term safety of secukinumab in patients with moderate-to-severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis: integrated pooled clinical trial and post-marketing surveillance data. *Arthritis Res. Ther.* 21:111. <https://doi.org/10.1186/s13075-019-1882-2>
- Doodles, P.D., Y. Cao, K.M. Hamel, Y. Wang, B. Farkas, Y. Iwakura, and A. Finnegan. 2008. Development of Proteoglycan-Induced Arthritis Is Independent of IL-17. *J. Immunol.* <https://doi.org/10.4049/jimmunol.181.1.329>
- Duarte, J., A. Agua-Doce, V.G. Oliveira, J.E. Fonseca, and L. Graca. 2010. Modulation of IL-17 and Foxp3 expression in the prevention of autoimmune arthritis in mice. *PLoS One.* 5:e10558. <https://doi.org/10.1371/journal.pone.0010558>
- Duerr, R.H., K.D. Taylor, S.R. Brant, J.D. Rioux, M.S. Silverberg, M.J. Daly, A.H. Steinhardt, C. Abraham, M. Regueiro, A. Griffiths, et al. 2006. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Science.* 314:1461–1463. <https://doi.org/10.1126/science.1135245>
- Eder, L., A. Haddad, C.F. Rosen, K.A. Lee, V. Chandran, R. Cook, and D.D. Gladman. 2016. The Incidence and Risk Factors for Psoriatic Arthritis in Patients With Psoriasis: A Prospective Cohort Study. *Arthritis Rheumatol.* 68:915–923. <https://doi.org/10.1002/art.39494>
- El-Behi, M., B. Ciric, H. Dai, Y. Yan, M. Cullimore, F. Safavi, G.X. Zhang, B.N. Dittel, and A. Rostami. 2011. The encephalitogenicity of T(H)17 cells is dependent on IL-1- and IL-23-induced production of the cytokine GM-CSF. *Nat. Immunol.* 12:568–575. <https://doi.org/10.1038/ni.2031>
- Elson, C.O., Y. Cong, C.T. Weaver, T.R. Schoeb, T.K. McClanahan, R.B. Fick, and R.A. Kastelein. 2007. Monoclonal anti-interleukin 23 reverses active colitis in a T cell-mediated model in mice. *Gastroenterology.* 132:2359–2370. <https://doi.org/10.1053/j.gastro.2007.03.104>
- Espugues, E., S. Huber, N. Gagliani, A.E. Hauser, T. Town, Y.Y. Wan, W. O'Connor Jr., A. Rongvaux, N. Van Rooijen, A.M. Haberman, et al. 2011. Control of Th17 cells occurs in the small intestine. *Nature.* 475:514–518. <https://doi.org/10.1038/nature10228>
- Feagan, B.G., W.J. Sandborn, G. D'Haens, J. Panés, A. Kaser, M. Ferrante, E. Louis, D. Franchimont, O. Dewit, U. Seidler, et al. 2017. Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study. *Lancet.* 389:1699–1709. [https://doi.org/10.1016/S0140-6736\(17\)30570-6](https://doi.org/10.1016/S0140-6736(17)30570-6)
- Feagan, B.G., J. Panés, M. Ferrante, A. Kaser, G.R. D'Haens, W.J. Sandborn, E. Louis, M.F. Neurath, D. Franchimont, O. Dewit, et al. 2018. Risankizumab in patients with moderate to severe Crohn's disease: an open-label extension study. *Lancet Gastroenterol. Hepatol.* 3:671–680. [https://doi.org/10.1016/S2468-1253\(18\)30233-4](https://doi.org/10.1016/S2468-1253(18)30233-4)
- Feng, T., H. Qin, L. Wang, E.N. Benveniste, C.O. Elson, and Y. Cong. 2011. Th17 cells induce colitis and promote Th1 cell responses through IL-17 induction of innate IL-12 and IL-23 production. *J. Immunol.* 186:6313–6318. <https://doi.org/10.4049/jimmunol.1001454>
- Ferretti, S., O. Bonneau, G.R. Dubois, C.E. Jones, and A. Trifilieff. 2003. IL-17, produced by lymphocytes and neutrophils, is necessary for lipopolysaccharide-induced airway neutrophilia: IL-15 as a possible trigger. *J. Immunol.* 170:2106–2112. <https://doi.org/10.4049/jimmunol.170.4.2106>
- Fossiez, F., O. Djossou, P. Chomarat, L. Flores-Romo, S. Ait-Yahia, C. Maat, J.J. Pin, P. Garrone, E. Garcia, S. Saeland, et al. 1996. T cell interleukin-17 induces stromal cells to produce proinflammatory and hematopoietic cytokines. *J. Exp. Med.* 183:2593–2603. <https://doi.org/10.1084/jem.183.6.2593>
- Fotiadiou, C., E. Lazaridou, E. Sotiriou, S. Gerou, A. Kyrgidis, E. Vakirlis, and D. Ioannides. 2015. IL-17A, IL-22, and IL-23 as markers of psoriasis activity: A cross-sectional, hospital-based study. *J. Cutan. Med. Surg.* 19:555–560. <https://doi.org/10.1177/1203475415584503>
- Fujino, S., A. Andoh, S. Bamba, A. Ogawa, K. Hata, Y. Araki, T. Bamba, and Y. Fujiyama. 2003. Increased expression of interleukin 17 in inflammatory bowel disease. *Gut.* 52:65–70. <https://doi.org/10.1136/gut.52.1.65>
- Genovese, M.C., M. Greenwald, C.S. Cho, A. Berman, L. Jin, G.S. Cameron, O. Benichou, L. Xie, D. Braun, P.Y. Berclaz, and S. Banerjee. 2014. A phase II randomized study of subcutaneous ixekizumab, an anti-interleukin-17 monoclonal antibody, in rheumatoid arthritis patients who were naive to biologic agents or had an inadequate response to tumor necrosis factor inhibitors. *Arthritis Rheumatol.* 66:1693–1704. <https://doi.org/10.1002/art.38617>
- Gocke, A.R., P.D. Cravens, L.-H. Ben, R.Z. Hussain, S.C. Northrop, M.K. Racke, and A.E. Lovett-Racke. 2007. T-bet Regulates the Fate of Th1 and Th17 Lymphocytes in Autoimmunity. *J. Immunol.* <https://doi.org/10.4049/jimmunol.178.3.1341>
- Gordon, K.B., A. Blauvelt, K.A. Papp, R.G. Langley, T. Luger, M. Ohtsuki, K. Reich, D. Amato, S.G. Ball, D.K. Braun, et al. UNCOVER-3 Study Group. 2016. Phase 3 Trials of Ixekizumab in Moderate-to-Severe Plaque Psoriasis. *N. Engl. J. Med.* 375:345–356. <https://doi.org/10.1056/NEJMoa1512711>
- Gordon, K.B., B. Strober, M. Lebwohl, M. Augustin, A. Blauvelt, Y. Poulin, K.A. Papp, H. Sofen, L. Puig, P. Foley, et al. 2018. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet.* 392:650–661. [https://doi.org/10.1016/S0140-6736\(18\)31713-6](https://doi.org/10.1016/S0140-6736(18)31713-6)
- Griffiths, C.E.M., K. Reich, M. Lebwohl, P. van de Kerkhof, C. Paul, A. Menter, G.S. Cameron, J. Erickson, L. Zhang, R.J. Secrest, et al. UNCOVER-2 and UNCOVER-3 investigators. 2015. Comparison of ixekizumab with

- etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet*. 386:541–551. [https://doi.org/10.1016/S0140-6736\(15\)60125-8](https://doi.org/10.1016/S0140-6736(15)60125-8)
- Gu, C., L. Wu, and X. Li. 2013. IL-17 family: cytokines, receptors and signaling. *Cytokine*. 64:477–485. <https://doi.org/10.1016/j.cyto.2013.07.022>
- Gyölvéssi, G., S. Haak, and B. Becher. 2009. IL-23-driven encephalo-tropism and Th17 polarization during CNS-inflammation in vivo. *Eur. J. Immunol.* 39:1864–1869. <https://doi.org/10.1002/eji.200939305>
- Haak, S., A.L. Croxford, K. Kreymerborg, F.L. Heppner, S. Pouly, B. Becher, and A. Waisman. 2009. IL-17A and IL-17F do not contribute vitally to autoimmune neuro-inflammation in mice. *J. Clin. Invest.* 119:61–69. <https://doi.org/10.1172/JCI35997>
- Happel, K.I., M. Zheng, E. Young, L.J. Quinton, E. Lockhart, A.J. Ramsay, J.E. Shellito, J.R. Schurr, G.J. Bagby, S. Nelson, and J.K. Kolls. 2003. Cutting edge: roles of Toll-like receptor 4 and IL-23 in IL-17 expression in response to *Klebsiella pneumoniae* infection. *J. Immunol.* 170:4432–4436. <https://doi.org/10.4049/jimmunol.170.9.4432>
- Havrdová, E., A. Belova, A. Goloborodko, A. Tisserant, A. Wright, E. Wallstroem, H. Garren, R.P. Maguire, and D.R. Johns. 2016. Activity of secukinumab, an anti-IL-17A antibody, on brain lesions in RRMS: results from a randomized, proof-of-concept study. *J. Neurol.* 263:1287–1295. <https://doi.org/10.1007/s00415-016-8128-x>
- He, D., L. Wu, H.K. Kim, H. Li, C.A. Elmets, and H. Xu. 2006. CD8+ IL-17-producing T cells are important in effector functions for the elicitation of contact hypersensitivity responses. *J. Immunol.* 177:6852–6858. <https://doi.org/10.4049/jimmunol.177.10.6852>
- Hirota, K., M. Hashimoto, H. Yoshitomi, S. Tanaka, T. Nomura, T. Yamaguchi, Y. Iwakura, N. Sakaguchi, and S. Sakaguchi. 2007. T cell self-reactivity forms a cytokine milieu for spontaneous development of IL-17+ Th cells that cause autoimmune arthritis. *J. Exp. Med.* 204:41–47. <https://doi.org/10.1084/jem.20062259>
- Hofstetter, H.H., S.M. Ibrahim, D. Koczan, N. Kruse, A. Weishaupt, K.V. Toyka, and R. Gold. 2005. Therapeutic efficacy of IL-17 neutralization in murine experimental autoimmune encephalomyelitis. *Cell. Immunol.* 237:123–130. <https://doi.org/10.1016/j.cellimm.2005.11.002>
- Holers, V.M., M.K. Demoruelle, K.A. Kuhn, J.H. Buckner, W.H. Robinson, Y. Okamoto, J.M. Norris, and K.D. Deane. 2018. Rheumatoid arthritis and the mucosal origins hypothesis: protection turns to destruction. *Nat. Rev. Rheumatol.* 14:542–557. <https://doi.org/10.1038/s41584-018-0070-0>
- Hölttä, V., P. Klemetti, T. Sipponen, M. Westerholm-Ormio, G. Kociubinski, H. Salo, L. Räsänen, K.L. Kolho, M. Färkkilä, E. Savilahti, and O. Vaarala. 2008. IL-23/IL-17 immunity as a hallmark of Crohn's disease. *Inflamm. Bowel Dis.* 14:1175–1184. <https://doi.org/10.1002/ibd.20475>
- Honorati, M.C., R. Meliconi, L. Pulsatelli, S. Canè, L. Frizziero, and A. Facchini. 2001. High in vivo expression of interleukin-17 receptor in synovial endothelial cells and chondrocytes from arthritis patients. *Rheumatology (Oxford)*. 40:522–527. <https://doi.org/10.1093/rheumatology/40.5.522>
- Hu, D., S. Notarbartolo, T. Croonenborghs, B. Patel, R. Cialic, T.H. Yang, D. Aschenbrenner, K.M. Andersson, M. Gattorno, M. Pham, et al. 2017. Transcriptional signature of human pro-inflammatory TH17 cells identifies reduced IL10 gene expression in multiple sclerosis. *Nat. Commun.* 8:1600. <https://doi.org/10.1038/s41467-017-01571-8>
- Hue, S., P. Ahern, S. Buonocore, M.C. Kullberg, D.J. Cua, B.S. McKenzie, F. Powrie, and K.J. Maloy. 2006. Interleukin-23 drives innate and T cell-mediated intestinal inflammation. *J. Exp. Med.* 203:2473–2483. <https://doi.org/10.1084/jem.20061099>
- Hueber, W., B.E. Sands, S. Lewitzky, M. Vandemeulebroecke, W. Reinisch, P.D.R. Higgins, J. Wehkamp, B.G. Feagan, M.D. Yao, M. Karczewski, et al. Secukinumab in Crohn's Disease Study Group. 2012. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. *Gut*. 61:1693–1700. <https://doi.org/10.1136/gutjnl-2011-301668>
- Ito, Y., T. Usui, S. Kobayashi, M. Iguchi-Hashimoto, H. Ito, H. Yoshitomi, T. Nakamura, M. Shimizu, D. Kawabata, N. Yukawa, et al. 2009. Gamma/delta T cells are the predominant source of interleukin-17 in affected joints in collagen-induced arthritis, but not in rheumatoid arthritis. *Arthritis Rheum.* 60:2294–2303. <https://doi.org/10.1002/art.24687>
- Ivanov, I.I., B.S. McKenzie, L. Zhou, C.E. Tadokoro, A. Lepelley, J.J. Lafaille, D.J. Cua, and D.R. Littman. 2006. The orphan nuclear receptor ROR-gamma-t directs the differentiation program of proinflammatory IL-17+ T helper cells. *Cell*. 126:1121–1133. <https://doi.org/10.1016/j.cell.2006.07.035>
- Ivanov, I.I., K. Atarashi, N. Manel, E.L. Brodie, T. Shima, U. Karaoz, D. Wei, K.C. Goldfarb, C.A. Santee, S.V. Lynch, et al. 2009. Induction of intestinal Th17 cells by segmented filamentous bacteria. *Cell*. 139:485–498. <https://doi.org/10.1016/j.cell.2009.09.033>
- Johansen, C., P.A. Usher, R.B. Kjellerup, D. Lundsgaard, L. Iversen, and K. Kragballe. 2009. Characterization of the interleukin-17 isoforms and receptors in lesional psoriatic skin. *Br. J. Dermatol.* 160:319–324. <https://doi.org/10.1111/j.1365-2133.2008.08902.x>
- Jørgensen, A.R., Y. Yao, and S.F. Thomsen. 2018. Therapeutic Response to Secukinumab in a 36-Year-Old Woman with Hidradenitis Suppurativa. *Case Rep. Dermatol. Med.* 2018:8685136. <https://doi.org/10.1155/2018/8685136>
- Jovanovic, D.V., J.A. Di Battista, J. Martel-Pelletier, F.C. Jolicœur, Y. He, M. Zhang, F. Mineau, and J.P. Pelletier. 1998. IL-17 stimulates the production and expression of proinflammatory cytokines, IL-beta and TNF-alpha, by human macrophages. *J. Immunol.* 160:3513–3521.
- Katayama, M., K. Ohmura, N. Yukawa, C. Terao, M. Hashimoto, H. Yoshifuji, D. Kawabata, T. Fujii, Y. Iwakura, and T. Mimori. 2013. Neutrophils are essential as a source of IL-17 in the effector phase of arthritis. *PLoS One*. 8:e62231. <https://doi.org/10.1371/journal.pone.0062231>
- Katt, J., D. Schwing, T. Schoknecht, A. Quaa, I. Sobottka, E. Burandt, C. Becker, M.F. Neurath, A.W. Lohse, J. Herkel, and C. Schramm. 2013. Increased T helper type 17 response to pathogen stimulation in patients with primary sclerosing cholangitis. *Hepatology*. 58:1084–1093. <https://doi.org/10.1002/hep.26447>
- Keffer, J., L. Probert, H. Cazarlis, S. Georgopoulos, E. Kaslaris, D. Kioussis, and G. Kollias. 1991. Transgenic mice expressing human tumour necrosis factor: a predictive genetic model of arthritis. *EMBO J.* 10:4025–4031. <https://doi.org/10.1002/j.1460-2075.1991.tb04978.x>
- Khatiri, A., B. Klünder, P.M. Peloso, and A.A. Othman. 2019. Exposure-response analyses demonstrate no evidence of interleukin 17A contribution to efficacy of ABT-122 in rheumatoid or psoriatic arthritis. *Rheumatology (Oxford)*. 58:352–360. <https://doi.org/10.1093/rheumatology/key312>
- Khattri, S., P.M. Brunner, S. Garcet, R. Finney, S.R. Cohen, M. Oliva, R. Dutt, J. Fuentes-Duculan, X. Zheng, X. Li, et al. 2017. Efficacy and safety of ustekinumab treatment in adults with moderate-to-severe atopic dermatitis. *Exp. Dermatol.* 26:28–35. <https://doi.org/10.1111/exd.13112>
- Kim, K.W., H.R. Kim, B.M. Kim, M.L. Cho, and S.H. Lee. 2015. Th17 cytokines regulate osteoclastogenesis in rheumatoid arthritis. *Am. J. Pathol.* 185:3011–3024. <https://doi.org/10.1016/j.ajpath.2015.07.017>
- Kinugasa, T., T. Sakaguchi, X. Gu, and H.C. Reinacker. 2000. Claudins regulate the intestinal barrier in response to immune mediators. *Gastroenterology*. 118:1001–1011. [https://doi.org/10.1016/S0016-5085\(00\)70351-9](https://doi.org/10.1016/S0016-5085(00)70351-9)
- Kirkham, B.W., M.N. Lassere, J.P. Edmonds, K.M. Juhasz, P.A. Bird, C.S. Lee, R. Shnier, and I.J. Portek. 2006. Synovial membrane cytokine expression is predictive of joint damage progression in rheumatoid arthritis: a two-year prospective study (the DAMAGE study cohort). *Arthritis Rheum.* 54:1122–1131. <https://doi.org/10.1002/art.21749>
- Kolbinger, F., C. Loesche, M.A. Valentin, X. Jiang, Y. Cheng, P. Jarvis, T. Peters, C. Calonder, G. Bruin, F. Polus, et al. 2017. β -Defensin 2 is a responsive biomarker of IL-17A-driven skin pathology in patients with psoriasis. *J. Allergy Clin. Immunol.* 139:923–932.e8. <https://doi.org/10.1016/j.jaci.2016.06.038>
- Komatsu, N., K. Okamoto, S. Sawa, T. Nakashima, M. Oh-hora, T. Kodama, S. Tanaka, J.A. Bluestone, and H. Takayanagi. 2014. Pathogenic conversion of Foxp3+ T cells into TH17 cells in autoimmune arthritis. *Nat. Med.* 20:62–68. <https://doi.org/10.1038/nm.3432>
- Komiyama, Y., S. Nakae, T. Matsuki, A. Nambu, H. Ishigame, S. Kakuta, K. Sudo, and Y. Iwakura. 2006. IL-17 plays an important role in the development of experimental autoimmune encephalomyelitis. *J. Immunol.* 177:566–573. <https://doi.org/10.4049/jimmunol.177.1.566>
- Komuczki, J., S. Tuzlak, E. Friebel, T. Hartwig, S. Spath, P. Rosenstiel, A. Waisman, L. Opitz, M. Oukka, B. Schreiner, et al. 2019. Fate-Mapping of GM-CSF Expression Identifies a Discrete Subset of Inflammation-Driving T Helper Cells Regulated by Cytokines IL-23 and IL-1 β . *Immunity*. 50:1289–1304.e6. <https://doi.org/10.1016/j.immuni.2019.04.006>
- Korn, T., E. Bettelli, M. Oukka, and V.K. Kuchroo. 2009. IL-17 and Th17 Cells. *Annu. Rev. Immunol.* 27:485–517. <https://doi.org/10.1146/annurev.immunol.021908.132710>
- Kostulas, N., S.H. Pelidou, P. Kivisäkk, V. Kostulas, and H. Link. 1999. Increased IL-1 β , IL-8, and IL-17 mRNA expression in blood mononuclear cells observed in a prospective ischemic stroke study. *Stroke*. 30:2174–2179. <https://doi.org/10.1161/01.STR.30.10.2174>

- Kotake, S., N. Udagawa, N. Takahashi, K. Matsuzaki, K. Itoh, S. Ishiyama, S. Saito, K. Inoue, N. Kamatani, M.T. Gillespie, et al. 1999. IL-17 in synovial fluids from patients with rheumatoid arthritis is a potent stimulator of osteoclastogenesis. *J. Clin. Invest.* 103:1345–1352. <https://doi.org/10.1172/JCI5703>
- Kulig, P., S. Musiol, S.N. Freiburger, B. Schreiner, G. Gyulveszi, G. Russo, S. Pantelyushin, K. Kishihara, F. Alessandrini, T. Kündig, et al. 2016. IL-12 protects from psoriasisform skin inflammation. *Nat. Commun.* 7:13466. <https://doi.org/10.1038/ncomms13466>
- Kumar, P., L. Monin, P. Castillo, W. Elsegeiny, W. Horne, T. Eddens, A. Vikram, M. Good, A.A. Schoenborn, K. Bibby, et al. 2016. Intestinal Interleukin-17 Receptor Signaling Mediates Reciprocal Control of the Gut Microbiota and Autoimmune Inflammation. *Immunity.* 44:659–671. <https://doi.org/10.1016/j.immuni.2016.02.007>
- Laggner, U., P. Di Meglio, G.K. Perera, C. Hundhausen, K.E. Lacy, N. Ali, C.H. Smith, A.C. Hayday, B.J. Nickoloff, and F.O. Nestle. 2011. Identification of a novel proinflammatory human skin-homing V γ 9V δ 2 T cell subset with a potential role in psoriasis. *J. Immunol.* 187:2783–2793. <https://doi.org/10.4049/jimmunol.1100804>
- Langley, R.G., B.E. Elewski, M. Lebwohl, K. Reich, C.E.M. Griffiths, K. Papp, L. Puig, H. Nakagawa, L. Spelman, B. Sigurgeirsson, et al. FIXTURE Study Group. 2014. Secukinumab in plaque psoriasis—results of two phase 3 trials. *N. Engl. J. Med.* 371:326–338. <https://doi.org/10.1056/NEJMoa1314258>
- Langley, R.G., T.-F. Tsai, S. Flavin, M. Song, B. Randazzo, Y. Wasfi, J. Jiang, S. Li, and L. Puig. 2018. Efficacy and safety of guselkumab in patients with psoriasis who have an inadequate response to ustekinumab: results of the randomized, double-blind, phase III NAVIGATE trial. *Br. J. Dermatol.* 178:114–123. <https://doi.org/10.1111/bjd.15750>
- Langley, R.G., A.B. Kimball, H. Nak, W. Xu, B. Pangallo, O.O. Osuntokun, N. Agada, and K. Reich. 2019. Long-term safety profile of ixekizumab in patients with moderate-to-severe plaque psoriasis: an integrated analysis from 11 clinical trials. *J. Eur. Acad. Dermatol. Venereol.* 33: 333–339. <https://doi.org/10.1111/jdv.15242>
- Langrish, C.L., Y. Chen, W.M. Blumenschein, J. Mattson, B. Basham, J.D. Sedgwick, T. McClanahan, R.A. Kastelein, and D.J. Cua. 2005. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. *J. Exp. Med.* 201:233–240. <https://doi.org/10.1084/jem.20041257>
- Lebwohl, M., B. Strober, A. Menter, K. Gordon, J. Weglowska, L. Puig, K. Papp, L. Spelman, D. Toth, F. Kerdel, et al. 2015. Phase 3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis. *N. Engl. J. Med.* 373:1318–1328. <https://doi.org/10.1056/NEJMoa1503824>
- Lee, Y., A. Awasthi, N. Yosef, F.J. Quintana, S. Xiao, A. Peters, C. Wu, M. Kleinewietfeld, S. Kunder, D.A. Hafler, et al. 2012. Induction and molecular signature of pathogenic TH17 cells. *Nat. Immunol.* 13:991–999. <https://doi.org/10.1038/ni.2416>
- Lee, J.S., C.M. Tato, B. Joyce-Shaikh, M.F. Gulen, C. Cayatte, Y. Chen, W.M. Blumenschein, M. Judo, G. Ayanoglu, T.K. McClanahan, et al. 2015. Interleukin-23-Independent IL-17 Production Regulates Intestinal Epithelial Permeability. *Immunity.* 43:727–738. <https://doi.org/10.1016/j.immuni.2015.09.003>
- Leijten, E.F.A., T.S. van Kempen, M. Boes, J.M.R. Michels-van Amelsfort, D. Hijnen, S.A.Y. Hartgring, J.A.G. van Roon, M.H. Wenink, and T.R.D.J. Radstake. 2015. Brief report: enrichment of activated group 3 innate lymphoid cells in psoriatic arthritis synovial fluid. *Arthritis Rheumatol.* 67:2673–2678. <https://doi.org/10.1002/art.39261>
- Leonardi, C.L., J.L. Powers, R.T. Matheson, B.S. Goffe, R. Zitnik, A. Wang, and A.B. Gottlieb. Etanercept Psoriasis Study Group. 2003. Etanercept as monotherapy in patients with psoriasis. *N. Engl. J. Med.* 349:2014–2022. <https://doi.org/10.1056/NEJMoa030409>
- Leonardi, S., C. Cuppari, S. Manti, M. Filippelli, G.F. Parisi, F. Borgia, S. Briuglia, P. Cannavò, A. Salpietro, T. Arrigo, and C. Salpietro. 2015. Serum interleukin 17, interleukin 23, and interleukin 10 values in children with atopic eczema/dermatitis syndrome (AEDS): association with clinical severity and phenotype. *Allergy Asthma Proc.* 36:74–81. <https://doi.org/10.2500/aap.2015.36.3808>
- Leppkes, M., C. Becker, I.I. Ivanov, S. Hirth, S. Wirtz, C. Neufert, S. Pouly, A.J. Murphy, D.M. Valenzuela, G.D. Yancopoulos, et al. 2009. RORgamma-expressing Th17 cells induce murine chronic intestinal inflammation via redundant effects of IL-17A and IL-17F. *Gastroenterology.* 136:257–267. <https://doi.org/10.1053/j.gastro.2008.10.018>
- Li, L., L. Huang, A.L. Vergis, H. Ye, A. Bajwa, V. Narayan, R.M. Strieter, D.L. Rosin, and M.D. Okusa. 2010. IL-17 produced by neutrophils regulates IFN- γ -mediated neutrophil migration in mouse kidney ischemia-reperfusion injury. *J. Clin. Invest.* 120:331–342. <https://doi.org/10.1172/JCI38702>
- Lin, A.M., C.J. Rubin, R. Khandpur, J.Y. Wang, M. Riblett, S. Yalavarthi, E.C. Villanueva, P. Shah, M.J. Kaplan, and A.T. Bruce. 2011. Mast cells and neutrophils release IL-17 through extracellular trap formation in psoriasis. *J. Immunol.* 187:490–500. <https://doi.org/10.4049/jimmunol.1100123>
- Linehan, J.L., O.J. Harrison, S.-J. Han, A.L. Byrd, I. Vujkovic-Cvijin, A.V. Villarino, S.K. Sen, J. Shaik, M. Smelkinson, S. Tamoutounour, et al. 2018. Non-classical Immunity Controls Microbiota Impact on Skin Immunity and Tissue Repair. *Cell.* 172:784–796.e18. <https://doi.org/10.1016/j.cell.2017.12.033>
- Liu, L., J. Lu, B.W. Allan, Y. Tang, J. Tetreault, C.K. Chow, B. Barmettler, J. Nelson, H. Bina, L. Huang, et al. 2016. Generation and characterization of ixekizumab, a humanized monoclonal antibody that neutralizes interleukin-17A. *J. Inflamm. Res.* 9:39–50. <https://doi.org/10.2147/JIR.S100940>
- Lubberts, E., L.A. Joosten, B. Oppers, L. van den Bersselaar, C.J. Coenen-de Roo, J.K. Kolls, P. Schwarzenberger, F.A. van de Loo, and W.B. van den Berg. 2001. IL-1-independent role of IL-17 in synovial inflammation and joint destruction during collagen-induced arthritis. *J. Immunol.* 167: 1004–1013. <https://doi.org/10.4049/jimmunol.167.2.1004>
- Lubberts, E., M.I. Koenders, B. Oppers-Walgreen, L. van den Bersselaar, C.J.J. Coenen-de Roo, L.A.B. Joosten, and W.B. van den Berg. 2004. Treatment with a neutralizing anti-murine interleukin-17 antibody after the onset of collagen-induced arthritis reduces joint inflammation, cartilage destruction, and bone erosion. *Arthritis Rheum.* 50:650–659. <https://doi.org/10.1002/art.20001>
- Lyman, M., V. Lieuw, R. Richardson, A. Timmer, C. Stewart, S. Granger, R. Woods, M. Silacci, D. Grabulovski, and R. Newman. 2018. A bispecific antibody that targets IL-6 receptor and IL-17A for the potential therapy of patients with autoimmune and inflammatory diseases. *J. Biol. Chem.* 293:9326–9334. <https://doi.org/10.1074/jbc.M117.818559>
- Malagoli, D. 2016. The evolution of the immune system: conservation and diversification. Elsevier, London. 384 pp.
- Mashiko, S., S. Bouguermouh, M. Rubio, N. Baba, R. Bissonnette, and M. Sarfati. 2015. Human mast cells are major IL-22 producers in patients with psoriasis and atopic dermatitis. *J. Allergy Clin. Immunol.* 136: 351–9.e1. <https://doi.org/10.1016/j.jaci.2015.01.033>
- Matusevicius, D., P. Kivisäkk, B. He, N. Kostulas, V. Özenci, S. Fredrikson, and H. Link. 1999. Interleukin-17 mRNA expression in blood and CSF mononuclear cells is augmented in multiple sclerosis. *Mult. Scler.* 5: 101–104. <https://doi.org/10.1177/135245859900500206>
- Maxwell, J.R., Y. Zhang, W.A. Brown, C.L. Smith, F.R. Byrne, M. Fiorino, E. Stevens, J. Bigler, J.A. Davis, J.B. Rottman, et al. 2015. Differential Roles for Interleukin-23 and Interleukin-17 in Intestinal Immunoregulation. *Immunity.* 43:739–750. <https://doi.org/10.1016/j.immuni.2015.08.019>
- McGeachy, M.J., and D.J. Cua. 2008. Th17 cell differentiation: the long and winding road. *Immunity.* 28:445–453. <https://doi.org/10.1016/j.immuni.2008.03.001>
- McGeachy, M.J., K.S. Bak-Jensen, Y. Chen, C.M. Tato, W. Blumenschein, T. McClanahan, and D.J. Cua. 2007. TGF- β and IL-6 drive the production of IL-17 and IL-10 by T cells and restrain T(H)-17 cell-mediated pathology. *Nat. Immunol.* 8:1390–1397. <https://doi.org/10.1038/nri1539>
- McGeachy, M.J., D.J. Cua, and S.L. Gaffen. 2019. The IL-17 Family of Cytokines in Health and Disease. *Immunity.* 50:892–906. <https://doi.org/10.1016/j.immuni.2019.03.021>
- McInnes, I.B., A. Kavanaugh, A.B. Gottlieb, L. Puig, P. Rahman, C. Ritchlin, C. Brodmerkel, S. Li, Y. Wang, A.M. Mendelsohn, and M.K. Doyle. PSUMMIT 1 Study Group. 2013. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. *Lancet.* 382:780–789. [https://doi.org/10.1016/S0140-6736\(13\)60594-2](https://doi.org/10.1016/S0140-6736(13)60594-2)
- McInnes, I.B., P.J. Mease, B. Kirkham, A. Kavanaugh, C.T. Ritchlin, P. Rahman, D. van der Heijde, R. Landewé, P.G. Conaghan, A.B. Gottlieb, et al. FUTURE 2 Study Group. 2015. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 386:1137–1146. [https://doi.org/10.1016/S0140-6736\(15\)61134-5](https://doi.org/10.1016/S0140-6736(15)61134-5)
- Mease, P.J., M.C. Genovese, M.W. Greenwald, C.T. Ritchlin, A.D. Beaulieu, A. Deodhar, R. Newmark, J. Feng, N. Erondou, and A. Nirula. 2014. Brodalumab, an anti-IL17RA monoclonal antibody, in psoriatic arthritis. *N. Engl. J. Med.* 370:2295–2306. <https://doi.org/10.1056/NEJMoa1315231>
- Mease, P.J., I.B. McInnes, B. Kirkham, A. Kavanaugh, P. Rahman, D. van der Heijde, R. Landewé, P. Nash, L. Pricop, J. Yuan, et al. FUTURE 1 Study

- Group. 2015. Secukinumab Inhibition of Interleukin-17A in Patients with Psoriatic Arthritis. *N. Engl. J. Med.* 373:1329–1339. <https://doi.org/10.1056/NEJMoal412679>
- Mease, P.J., D. van der Heijde, C.T. Ritchlin, M. Okada, R.S. Cuchacovich, C.L. Shuler, C.-Y. Lin, D.K. Braun, C.H. Lee, and D.D. Gladman. SPIRIT-P1 Study Group. 2017. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naïve patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. *Ann. Rheum. Dis.* 76:79–87. <https://doi.org/10.1136/annrheumdis-2016-209709>
- Mease, P.J., M.C. Genovese, M.E. Weinblatt, P.M. Peloso, K. Chen, A.A. Othman, Y. Li, H.T. Mansikka, A. Khatri, N. Wishart, and J. Liu. 2018a. Phase II Study of ABT-122, a Tumor Necrosis Factor- and Interleukin-17A-Targeted Dual Variable Domain Immunoglobulin, in Patients With Psoriatic Arthritis With an Inadequate Response to Methotrexate. *Arthritis Rheumatol.* 70:1778–1789. <https://doi.org/10.1002/art.40579>
- Mease, P.J., S. Jeka, J.J. Jaller, T. Kitumnuaypong, W. Louthrenoo, H. Mann, G. Matsievskaia, E.R. Soriano, B. Jia, C. Wang, et al. 2018b. CNTO6785, a fully human anti-Interleukin 17 monoclonal antibody, in patients with rheumatoid arthritis with inadequate response to methotrexate: A randomized, placebo-controlled, phase II, dose-ranging study. *J. Rheumatol.* 45:22–31. <https://doi.org/10.3899/jrheum.161238>
- Mease, P., E. Roussou, G.-R. Burmester, P. Goupille, A. Gottlieb, S.R. Moriarty, O. Benichou, D.H. Adams, W. Xu, and P. Nash. 2019. Safety of Ixekizumab in Patients With Psoriatic Arthritis: Results From a Pooled Analysis of Three Clinical Trials. *Arthritis Care Res. (Hoboken)*. 71: 367–378. <https://doi.org/10.1002/acr.23738>
- Menon, B., N.J. Gullick, G.J. Walter, M. Rajasekhar, T. Garrood, H.G. Evans, L.S. Taams, and B.W. Kirkham. 2014. Interleukin-17+CD8+ T cells are enriched in the joints of patients with psoriatic arthritis and correlate with disease activity and joint damage progression. *Arthritis Rheumatol.* 66:1272–1281. <https://doi.org/10.1002/art.38376>
- Michel, M.-L., A.C. Keller, C. Paget, M. Fujio, F. Trottein, P.B. Savage, C.-H. Wong, E. Schneider, M. Dy, and M.C. Leite-de-Moraes. 2007. Identification of an IL-17-producing NK1.1(neg) iNKT cell population involved in airway neutrophilia. *J. Exp. Med.* 204:995–1001. <https://doi.org/10.1084/jem.20061551>
- Monin, L., and S.L. Gaffen. 2018. Interleukin 17 Family Cytokines : Signaling and Therapeutic Implications. *Cold Spring Harb. Perspect. Biol.* 10. <https://doi.org/10.1101/cshperspect.a028522>
- Mosmann, T.R., H. Cherwinski, M.W. Bond, M.A. Giedlin, and R.L. Coffman. 1986. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J. Immunol.* 136: 2348–2357.
- Naik, S., N. Bouladoux, J.L. Linehan, S.J. Han, O.J. Harrison, C. Wilhelm, S. Conlan, S. Himmelfarb, A.L. Byrd, C. Deming, et al. 2015. Commensal-dendritic-cell interaction specifies a unique protective skin immune signature. *Nature*. 520:104–108. <https://doi.org/10.1038/nature14052>
- Naik, S., S.B. Larsen, N.C. Gomez, K. Alavertyan, A. Sendoel, S. Yuan, L. Polak, A. Kulukian, S. Chai, and E. Fuchs. 2017. Inflammatory memory sensitizes skin epithelial stem cells to tissue damage. *Nature*. 550: 475–480. <https://doi.org/10.1038/nature24271>
- Nakae, S., A. Nambu, K. Sudo, and Y. Iwakura. 2003. Suppression of immune induction of collagen-induced arthritis in IL-17-deficient mice. *J. Immunol.* 171:6173–6177. <https://doi.org/10.4049/jimmunol.171.11.6173>
- Nash, P., B. Kirkham, M. Okada, P. Rahman, B. Combe, G.R. Burmester, D.H. Adams, L. Kerr, C. Lee, C.L. Shuler, and M. Genovese. SPIRIT-P2 Study Group. 2017. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. *Lancet*. 389:2317–2327. [https://doi.org/10.1016/S0140-6736\(17\)31429-0](https://doi.org/10.1016/S0140-6736(17)31429-0)
- Nestle, F.O., C. Conrad, A. Tun-Kyi, B. Homey, M. Gombert, O. Boyman, G. Burg, Y.-J. Liu, and M. Gilliet. 2005. Plasmacytoid predendritic cells initiate psoriasis through interferon- α production. *J. Exp. Med.* 202: 135–143. <https://doi.org/10.1084/jem.20050500>
- Nikaein, A., C. Phillips, S.C. Gilbert, D. Savino, A. Silverman, M.J. Stone, and A. Menter. 1991. Characterization of skin-infiltrating lymphocytes in patients with psoriasis. *J. Invest. Dermatol.* 96:3–9. <https://doi.org/10.1111/1523-1747.ep12514646>
- O'Connor, W. Jr., M. Kamanaka, C.J. Booth, T. Town, S. Nakae, Y. Iwakura, J.K. Kolls, and R.A. Flavell. 2009. A protective function for interleukin 17A in T cell-mediated intestinal inflammation. *Nat. Immunol.* 10: 603–609. <https://doi.org/10.1038/ni.1736>
- Ogawa, A., A. Andoh, Y. Araki, T. Bamba, and Y. Fujiyama. 2004. Neutralization of interleukin-17 aggravates dextran sulfate sodium-induced colitis in mice. *Clin. Immunol.* 110:55–62. <https://doi.org/10.1016/j.clim.2003.09.013>
- Okada, S., A. Puel, J.-L. Casanova, and M. Kobayashi. 2016. Chronic mucocutaneous candidiasis disease associated with inborn errors of IL-17 immunity. *Clin. Transl. Immunology*. 5:e114. <https://doi.org/10.1038/cti.2016.71>
- Onishi, R.M., and S.L. Gaffen. 2010. Interleukin-17 and its target genes: mechanisms of interleukin-17 function in disease. *Immunology*. 129: 311–321. <https://doi.org/10.1111/j.1365-2567.2009.03240.x>
- Ortega, C., S. Fernández-A, J.M. Carrillo, P. Romero, I.J. Molina, J.C. Moreno, and M. Santamaría. 2009. IL-17-producing CD8+ T lymphocytes from psoriasis skin plaques are cytotoxic effector cells that secrete Th17-related cytokines. *J. Leukoc. Biol.* 86:435–443. <https://doi.org/10.1189/JLB.0109046>
- Osta, B., J.P. Roux, F. Lavocat, M. Pierre, N. Ndongo-Thiam, G. Boivin, and P. Miossec. 2015. Differential effects of IL-17A and TNF- α on osteoblastic differentiation of isolated synoviocytes and on bone explants from arthritis patients. *Front. Immunol.* 6:151. <https://doi.org/10.3389/fimmu.2015.00151>
- Panitch, H.S., R.L. Hirsch, J. Schindler, and K.P. Johnson. 1987. Treatment of multiple sclerosis with gamma interferon: exacerbations associated with activation of the immune system. *Neurology*. 37:1097–1102. <https://doi.org/10.1212/WNL.37.7.1097>
- Pantelyushin, S., S. Haak, B. Ingold, P. Kulig, F.L. Heppner, A.A. Navarini, and B. Becher. 2012. Roryt+ innate lymphocytes and $\gamma\delta$ T cells initiate psoriasis plaque formation in mice. *J. Clin. Invest.* 122:2252–2256. <https://doi.org/10.1172/JCI61862>
- Papp, K.A., R.G. Langley, M. Lebwohl, G.G. Krueger, P. Szapary, N. Yeilding, C. Guzzo, M.C. Hsu, Y. Wang, S. Li, et al. PHOENIX 2 study investigators. 2008. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet*. 371:1675–1684. [https://doi.org/10.1016/S0140-6736\(08\)60726-6](https://doi.org/10.1016/S0140-6736(08)60726-6)
- Papp, K.A., K. Reich, C. Paul, A. Blauvelt, W. Baran, C. Bolduc, D. Toth, R.G. Langley, J. Cather, A.B. Gottlieb, et al. 2016. A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. *Br. J. Dermatol.* 175: 273–286. <https://doi.org/10.1111/bjd.14493>
- Park, H., Z. Li, X.O. Yang, S.H. Chang, R. Nurieva, Y.H. Wang, Y. Wang, L. Hood, Z. Zhu, Q. Tian, and C. Dong. 2005. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. *Nat. Immunol.* 6:1133–1141. <https://doi.org/10.1038/ni1261>
- Passos, S.T., J.S. Silver, A.C. O'Hara, D. Sehy, J.S. Stumhofer, and C.A. Hunter. 2010. IL-6 promotes NK cell production of IL-17 during toxoplasmosis. *J. Immunol.* 184:1776–1783. <https://doi.org/10.4049/jimmunol.0901843>
- Paul, C., C.E.M. Griffiths, P.C.M. van de Kerkhof, L. Puig, Y. Dutronc, C. Henneges, M. Dossentbach, K. Hollister, and K. Reich. 2019. Ixekizumab provides superior efficacy compared with ustekinumab over 52 weeks of treatment: Results from IXORA-S, a phase 3 study. *J. Am. Acad. Dermatol.* 80:70–79.e3. <https://doi.org/10.1016/j.jaad.2018.06.039>
- Pavelka, K., Y. Chon, R. Newmark, S.-L. Lin, S. Baumgartner, and N. Eröndu. 2015. A study to evaluate the safety, tolerability, and efficacy of brodalumab in subjects with rheumatoid arthritis and an inadequate response to methotrexate. *J. Rheumatol.* 42:912–919. <https://doi.org/10.3899/jrheum.141271>
- Perera, G.K., P. Di Meglio, and F.O. Nestle. 2012. Psoriasis. *Annu. Rev. Pathol.* 7: 385–422. <https://doi.org/10.1146/annurev-pathol-011811-132448>
- Pfeifle, R., T. Rothe, N. Ipseiz, H.U. Scherer, S. Culemann, U. Harre, J.A. Ackermann, M. Seefried, A. Kleyer, S. Uderhardt, et al. 2017. Regulation of autoantibody activity by the IL-23-T_H17 axis determines the onset of autoimmune disease. *Nat. Immunol.* 18:104–113. <https://doi.org/10.1038/ni.3579>
- Raphael, I., S. Nalawade, T.N. Eagar, and T.G. Forsthuber. 2015. T cell subsets and their signature cytokines in autoimmune and inflammatory diseases. *Cytokine*. 74:5–17. <https://doi.org/10.1016/j.cyto.2014.09.011>
- Reich, K., K.A. Papp, A. Blauvelt, S.K. Tying, R. Sinclair, D. Thaçi, K. Nogales, A. Mehta, N. Cichanowitz, Q. Li, et al. 2017. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. *Lancet*. 390:276–288. [https://doi.org/10.1016/S0140-6736\(17\)31279-5](https://doi.org/10.1016/S0140-6736(17)31279-5)
- Ritchlin, C.T., R.A. Colbert, and D.D. Gladman. 2017. Psoriatic Arthritis. *N. Engl. J. Med.* 376:957–970. <https://doi.org/10.1056/NEJMra1505557>

- Rouvier, E., M.F. Luciani, M.G. Mattéi, F. Denizot, and P. Golstein. 1993. CTLA-8, cloned from an activated T cell, bearing AU-rich messenger RNA instability sequences, and homologous to a herpesvirus saimiri gene. *J. Immunol.* 150:5445–5456.
- Saeki, H., K. Kabashima, Y. Tokura, Y. Murata, A. Shiraishi, R. Tamamura, B. Randazzo, and K. Imanaka. 2017. Efficacy and safety of ustekinumab in Japanese patients with severe atopic dermatitis: a randomized, double-blind, placebo-controlled, phase II study. *Br. J. Dermatol.* 177:419–427. <https://doi.org/10.1111/bjd.15493>
- Sallusto, F., C.E. Zielinski, and A. Lanzavecchia. 2012. Human Th17 subsets. *Eur. J. Immunol.* 42:2215–2220. <https://doi.org/10.1002/eji.201242741>
- Sands, B.E., J. Chen, B.G. Feagan, M. Penney, W.A. Rees, S. Danese, P.D.R. Higgins, P. Newbold, K. Okamoto, A. Yamaguchi, K. Patra, et al. 2017. Efficacy and Safety of MEDI2070, an Antibody Against Interleukin 23, in Patients With Moderate to Severe Crohn's Disease: A Phase 2a Study. *Gastroenterology.* 153:77–86.e6. <https://doi.org/10.1053/j.gastro.2017.03.049>
- Sato, K., A. Suematsu, K. Okamoto, A. Yamaguchi, Y. Morishita, Y. Kadono, S. Tanaka, T. Kodama, S. Akira, Y. Iwakura, et al. 2006. Th17 functions as an osteoclastogenic helper T cell subset that links T cell activation and bone destruction. *J. Exp. Med.* 203:2673–2682. <https://doi.org/10.1084/jem.20061775>
- Saunte, D.M., U. Mrowietz, L. Puig, and C. Zachariae. 2017. Candida infections in patients with psoriasis and psoriatic arthritis treated with interleukin-17 inhibitors and their practical management. *Br. J. Dermatol.* 177:47–62. <https://doi.org/10.1111/bjd.15015>
- Sawyer, L.M., L. Cornic, L.A. Levin, C. Gibbons, A.H. Møller, and G.B. Jemec. 2019. Long-term efficacy of novel therapies in moderate-to-severe plaque psoriasis: a systematic review and network meta-analysis of PASI response. *J. Eur. Acad. Dermatol. Venereol.* 33:355–366. <https://doi.org/10.1111/jdv.15277>
- Schlegel, P.M., I. Steiert, I. Kötter, and C.A. Müller. 2013. B cells contribute to heterogeneity of IL-17 producing cells in rheumatoid arthritis and healthy controls. *PLoS One.* 8:e82580. <https://doi.org/10.1371/journal.pone.0082580>
- Schreiber, S., J.-F. Colombel, B.G. Feagan, K. Reich, A.A. Deodhar, I.B. McInnes, B. Porter, A. Das Gupta, L. Pricop, and T. Fox. 2019. Incidence rates of inflammatory bowel disease in patients with psoriasis, psoriatic arthritis and ankylosing spondylitis treated with secukinumab: a retrospective analysis of pooled data from 21 clinical trials. *Ann. Rheum. Dis.* 78:473–479. <https://doi.org/10.1136/annrheumdis-2018-214273>
- Scott, D.L., F. Wolfe, and T.W.J. Huizinga. 2010. Rheumatoid arthritis. *Lancet.* 376:1094–1108. [https://doi.org/10.1016/S0140-6736\(10\)60826-4](https://doi.org/10.1016/S0140-6736(10)60826-4)
- Segal, B.M., C.S. Constantinescu, A. Raychaudhuri, L. Kim, R. Fidelus-Gort, and L.H. Kasper. Ustekinumab MS Investigators. 2008. Repeated subcutaneous injections of IL12/23 p40 neutralising antibody, ustekinumab, in patients with relapsing-remitting multiple sclerosis: a phase II, double-blind, placebo-controlled, randomised, dose-ranging study. *Lancet Neurol.* 7:796–804. [https://doi.org/10.1016/S1474-4422\(08\)70173-X](https://doi.org/10.1016/S1474-4422(08)70173-X)
- Shalom-Barak, T., J. Quach, and M. Lotz. 1998. Interleukin-17-induced gene expression in articular chondrocytes is associated with activation of mitogen-activated protein kinases and NF-kappaB. *J. Biol. Chem.* 273:27467–27473. <https://doi.org/10.1074/jbc.273.42.27467>
- Shen, F., M.J. Ruddy, P. Plamondon, and S.L. Gaffen. 2005. Cytokines link osteoblasts and inflammation: microarray analysis of interleukin-17- and TNF- α -induced genes in bone cells. *J. Leukoc. Biol.* 77:388–399. <https://doi.org/10.1189/jlb.0904490>
- Smolen, J.S., S.K. Agarwal, E. Ilivanova, X.L. Xu, Y. Miao, Y. Zhuang, I. Nnane, W. Radziszewski, A. Greenspan, A. Beutler, and D. Baker. 2017. A randomised phase II study evaluating the efficacy and safety of subcutaneously administered ustekinumab and guselkumab in patients with active rheumatoid arthritis despite treatment with methotrexate. *Ann. Rheum. Dis.* 76:831–839. <https://doi.org/10.1136/annrheumdis-2016-209831>
- Song, C., L. Luo, Z. Lei, B. Li, Z. Liang, G. Liu, D. Li, G. Zhang, B. Huang, and Z.-H. Feng. 2008. IL-17-Producing Alveolar Macrophages Mediate Allergic Lung Inflammation Related to Asthma. *J. Immunol.* 181:6117–6124. <https://doi.org/10.4049/jimmunol.181.9.6117>
- Song, X., D. Dai, X. He, S. Zhu, Y. Yao, H. Gao, J. Wang, F. Qu, J. Qiu, H. Wang, et al. 2015. Growth Factor FGF2 Cooperates with Interleukin-17 to Repair Intestinal Epithelial Damage. *Immunity.* 43:488–501. <https://doi.org/10.1016/j.immuni.2015.06.024>
- Sparber, F., C. De Gregorio, S. Steckholzer, F.M. Ferreira, T. Dolowschiak, F. Ruchti, F.R. Kirchner, S. Mertens, I. Prinz, N. Joller, et al. 2019. The Skin Commensal Yeast *Malassezia* Triggers a Type 17 Response that Coordinates Anti-fungal Immunity and Exacerbates Skin Inflammation. *Cell Host Microbe.* 25:389–403.e6. <https://doi.org/10.1016/j.chom.2019.02.002>
- Spath, S., J. Komuczki, M. Hermann, P. Pelczar, F. Mair, B. Schreiner, and B. Becher. 2017. Dysregulation of the Cytokine GM-CSF Induces Spontaneous Phagocyte Invasion and Immunopathology in the Central Nervous System. *Immunity.* 46:245–260. <https://doi.org/10.1016/j.immuni.2017.01.007>
- Sutton, C.E., S.J. Lalor, C.M. Sweeney, C.F. Brereton, E.C. Lavelle, and K.H.G. Mills. 2009. Interleukin-1 and IL-23 induce innate IL-17 production from gammadelta T cells, amplifying Th17 responses and autoimmunity. *Immunity.* 31:331–341. <https://doi.org/10.1016/j.immuni.2009.08.001>
- Takahashi, N., I. Vanlaere, R. de Rycke, A. Cauwels, L.A. Joosten, E. Lubberts, W.B. van den Berg, and C. Libert. 2008. IL-17 produced by Paneth cells drives TNF-induced shock. *J. Exp. Med.* 205:1755–1761. <https://doi.org/10.1084/jem.20080588>
- Tamassia, N., F. Arruda-Silva, F. Calzetti, S. Lonardi, S. Gasperini, E. Gardiman, F. Bianchetto-Aguilera, L.B. Gatta, G. Girolomoni, A. Mantovani, et al. 2018. A reappraisal on the potential ability of human neutrophils to express and produce IL-17 family members in vitro: Failure to reproducibly detect it. *Front. Immunol.* 9:795. <https://doi.org/10.3389/fimmu.2018.00795>
- Tang, C., S. Kakuta, K. Shimizu, M. Kadoki, T. Kamiya, T. Shimazu, S. Kubo, S. Saijo, H. Ishigame, S. Nakae, and Y. Iwakura. 2018. Suppression of IL-17F, but not of IL-17A, provides protection against colitis by inducing T_{reg} cells through modification of the intestinal microbiota. *Nat. Immunol.* 19:755–765. <https://doi.org/10.1038/s41590-018-0134-y>
- Targan, S.R., B. Feagan, S. Vermeire, R. Panaccione, G.Y. Melmed, C. Landers, D. Li, C. Russell, R. Newmark, N. Zhang, et al. 2016. A randomized, double-blind, placebo-controlled phase 2 study of brodalumab in patients with moderate-to-severe Crohn's disease. *Am. J. Gastroenterol.* 111:1599–1607. <https://doi.org/10.1038/ajg.2016.298>
- Tonel, G., C. Conrad, U. Laggner, P. Di Meglio, K. Grys, T.K. McClanahan, W.M. Blumenschein, J.-Z. Qin, H. Xin, E. Oldham, et al. 2010. Cutting edge: A critical functional role for IL-23 in psoriasis. *J. Immunol.* 185:5688–5691. <https://doi.org/10.4049/jimmunol.1001538>
- Tzartos, J.S., M.A. Friese, M.J. Craner, J. Palace, J. Newcombe, M.M. Esiri, and L. Fugger. 2008. Interleukin-17 production in central nervous system-infiltrating T cells and glial cells is associated with active disease in multiple sclerosis. *Am. J. Pathol.* 172:146–155. <https://doi.org/10.2353/ajpath.2008.070690>
- van der Fits, L., S. Mourits, J.S.A. Voerman, M. Kant, L. Boon, J.D. Laman, F. Cornelissen, A.-M. Mus, E. Florencia, E.P. Prens, and E. Lubberts. 2009. Imiquimod-induced psoriasis-like skin inflammation in mice is mediated via the IL-23/IL-17 axis. *J. Immunol.* 182:5836–5845. <https://doi.org/10.4049/jimmunol.0802999>
- van der Heijde, D., J. Cheng-Chung Wei, M. Dougados, P. Mease, A. Deodhar, W.P. Maksymowych, F. Van den Bosch, J. Sieper, T. Tomita, R. Landewé, et al. COAST-V study group. 2018. Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial. *Lancet.* 392:2441–2451. [https://doi.org/10.1016/S0140-6736\(18\)31946-9](https://doi.org/10.1016/S0140-6736(18)31946-9)
- van Tok, M.N., S. Na, C.R. Lao, M. Alvi, D. Pots, M.G.H. van de Sande, J.D. Taurog, J.D. Sedgwick, D.L. Baeten, and L.M. van Duivenvoorde. 2018. The Initiation, but Not the Persistence, of Experimental Spondyloarthritis Is Dependent on Interleukin-23 Signaling. *Front. Immunol.* 9:1550. <https://doi.org/10.3389/fimmu.2018.01550>
- Vazquez-Tello, A., R. Halwani, R. Li, J. Nadigel, A. Bar-Or, B.D. Mazer, D.H. Eidelman, S. Al-Muhsen, and Q. Hamid. 2012. IL-17A and IL-17F expression in B lymphocytes. *Int. Arch. Allergy Immunol.* 157:406–416. <https://doi.org/10.1159/000329527>
- Veldhoen, M., R.J. Hocking, C.J. Atkins, R.M. Locksley, and B. Stockinger. 2006. TGF β in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells. *Immunity.* 24:179–189. <https://doi.org/10.1016/j.immuni.2006.01.001>
- Villani, A.P., M. Rouzaud, M. Sevrain, T. Barnetche, C. Paul, M.A. Richard, M. Beylot-Barry, L. Misery, P. Joly, M. Le Maitre, et al. 2015. Prevalence of undiagnosed psoriatic arthritis among psoriasis patients: Systematic review and meta-analysis. *J. Am. Acad. Dermatol.* 73:242–248. <https://doi.org/10.1016/j.jaad.2015.05.001>

- Vollmer, T.L., D.R. Wynn, M.S. Alam, and J. Valdes. 2011. A phase 2, 24-week, randomized, placebo-controlled, double-blind study examining the efficacy and safety of an anti-interleukin-12 and -23 monoclonal antibody in patients with relapsing-remitting or secondary progressive multiple sclerosis. *Mult. Scler.* 17:181-191. <https://doi.org/10.1177/1352458510384496>
- Wain, T., B. Choy, A.C. Satchell, J.A. Woods, and J.W. Frew. 2018. Secukinumab in pityriasis rubra pilaris: A case series demonstrating variable response and the need for minimal clinical datasets. *JAAD Case Rep.* 4: 500-505. <https://doi.org/10.1016/j.jidcr.2018.02.007>
- Wright, J.F., Y. Guo, A. Quazi, D.P. Luxenberg, F. Bennett, J.F. Ross, Y. Qiu, M.J. Whitters, K.N. Tomkinson, K. Dunussi-Joannopoulos, et al. 2007. Identification of an interleukin 17F/17A heterodimer in activated human CD4+ T cells. *J. Biol. Chem.* 282:13447-13455. <https://doi.org/10.1074/jbc.M700499200>
- Wu, H.-J., I.I. Ivanov, J. Darce, K. Hattori, T. Shima, Y. Umesaki, D.R. Littman, C. Benoist, and D. Mathis. 2010. Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells. *Immunity.* 32: 815-827. <https://doi.org/10.1016/j.immuni.2010.06.001>
- Xu, S., and X. Cao. 2010. Interleukin-17 and its expanding biological functions. *Cell. Mol. Immunol.* 7:164-174. <https://doi.org/10.1038/cmi.2010.21>
- Yamamoto, M., K. Nakajima, M. Takaishi, S. Kitaba, Y. Magata, S. Kataoka, and S. Sano. 2015. Psoriatic inflammation facilitates the onset of arthritis in a mouse model. *J. Invest. Dermatol.* 135:445-453. <https://doi.org/10.1038/jid.2014.426>
- Yang, Y., J. Weiner, Y. Liu, A.J. Smith, D.J. Huss, R. Winger, H. Peng, P.D. Cravens, M.K. Racke, and A.E. Lovett-Racke. 2009. T-bet is essential for encephalitogenicity of both Th1 and Th17 cells. *J. Exp. Med.* 206: 1549-1564. <https://doi.org/10.1084/jem.20082584>
- Yao, Z., W.C. Fanslow, M.F. Seldin, A.M. Rousseau, S.L. Painter, M.R. Co-meau, J.I. Cohen, and M.K. Spriggs. 1995a. Herpesvirus Saimiri encodes a new cytokine, IL-17, which binds to a novel cytokine receptor. *Immunity.* 3:811-821. [https://doi.org/10.1016/1074-7613\(95\)90070-5](https://doi.org/10.1016/1074-7613(95)90070-5)
- Yao, Z., S.L. Painter, W.C. Fanslow, D. Ulrich, B.M. Macduff, M.K. Spriggs, and R.J. Armitage. 1995b. Human IL-17: a novel cytokine derived from T cells. *J. Immunol.* 155:5483-5486.
- Yen, D., J. Cheung, H. Scheerens, F. Poulet, T. McClanahan, B. McKenzie, M.A. Kleinschek, A. Owyang, J. Mattson, W. Blumenschein, et al. 2006. IL-23 is essential for T cell-mediated colitis and promotes inflammation via IL-17 and IL-6. *J. Clin. Invest.* 116:1310-1316. <https://doi.org/10.1172/JCI21404>
- Zenz, R., R. Eferl, L. Kenner, L. Florin, L. Hummerich, D. Mehic, H. Scheuch, P. Angel, E. Tschachler, and E.F. Wagner. 2005. Psoriasis-like skin disease and arthritis caused by inducible epidermal deletion of Jun proteins. *Nature.* 437:369-375. <https://doi.org/10.1038/nature03963>
- Zhang, L.-W., P.-R. Zhou, P. Wei, X. Cong, L.-L. Wu, and H. Hua. 2018. Expression of interleukin-17 in primary Sjögren's syndrome and the correlation with disease severity: A systematic review and meta-analysis. *Scand. J. Immunol.* 87:e12649. <https://doi.org/10.1111/sji.12649>
- Zheng, Y., P.A. Valdez, D.M. Danilenko, Y. Hu, S.M. Sa, Q. Gong, A.R. Abbas, Z. Modrusan, N. Ghilardi, F.J. de Sauvage, and W. Ouyang. 2008. Interleukin-22 mediates early host defense against attaching and effacing bacterial pathogens. *Nat. Med.* 14:282-289. <https://doi.org/10.1038/nm1720>
- Ziolkowska, M., A. Koc, G. Luszczkiewicz, K. Ksiezopolska-Pietrzak, E. Klimczak, H. Chwalinska-Sadowska, and W. Maslinski. 2000. High levels of IL-17 in rheumatoid arthritis patients: IL-15 triggers in vitro IL-17 production via cyclosporin A-sensitive mechanism. *J. Immunol.* 164: 2832-2838. <https://doi.org/10.4049/jimmunol.164.5.2832>