Published in final edited form as:

Curr Opin Immunol. 2018 December ; 55: 9–14. doi:10.1016/j.coi.2018.09.002.

IL-6: A cytokine at the crossroads of autoimmunity

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Abstract

IL-6 is implicated in the development and progression of autoimmune diseases in part by influencing CD4 T cell lineage and regulation. Elevated IL-6 levels drive inflammation in a wide range of autoimmune diseases, some of which are also characterized by enhanced T cell responses to IL-6. Notably, the impact of IL-6 on inflammation is contextual in nature and dependent on the cell type, cytokine milieu and tissue. Targeting the IL-6/IL-6R axis in humans has been shown to successfully ameliorate a subset of autoimmune conditions. In this review, we discuss recent studies investigating how IL-6 regulates the CD4 T cell response in the context of autoimmune disease and highlight how blocking different aspects of the IL-6 pathway is advantageous in the treatment of disease.

Introduction

Interleukin-6 (IL-6) is a pleiotropic cytokine involved in chronic inflammation, autoantibody production, vascular permeability as well as tissue regeneration, metabolism and hematopoiesis. IL-6 is produced by stromal cells, monocytes and lymphocytes, and its expression is increased by IL-1β, TNF-α, as well as stimulation of Toll-like receptors and additional stress response proteins [1]. Elevated IL-6 serum and tissue concentrations are a hallmark of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and relapsing-remitting multiple sclerosis (MS), often correlating with disease activity [2–4]. IL-6 signals via three mechanisms: classic, trans- and cluster signaling, each of which lead to distinct immune outcomes. The role of IL-6 in the adaptive immune response is diverse, providing both proinflammatory and immunoregulatory signals based on the cell type, cytokine milieu and the manner through which it is sensed [5]. In this review, we will discuss how the IL-6 signaling pathway influences the adaptive immune response, promotes autoimmunity and how blocking different aspects of this pathway is advantageous in the treatment of disease.

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IL-6 promotes Th17 and Tfh cell development while suppressing Treg induction

IL-6 contributes to the development of autoreactive proinflammatory CD4 T cell responses by promoting Th17 cell lineage and function, and by inhibiting the induction of regulatory T cells (Treg) (Figure 1). Th17 cells have been implicated in the pathogenesis of RA, MS, type 1 diabetes (T1D) and SLE [6,7]. IL-6 in combination with TGF-β promotes the development and function of Th17 cells [8], and in mice, IL-6 promotes the expansion of Th17 cells [9]. In addition, a recent study by Zhao *et al* reports that IL-6 stimulation inhibits expression of RFX1, a transcriptional repressor of IL-17A production in CD4+ T cells [10]. IL-6 also influences Th17 cells via regulation of microRNAs; IL-6 induces miR-183c, which promotes Th17 pathogenicity via upregulation of IL-1R1 [11].

IL-6 is implicated in the regulation of T cell responses both by inhibiting the generation of Foxp3+ Tregs and promoting effector CD4 T cells (Teff) resistant to suppression [8,12–14]. IL-6R is highly expressed on Tregs; it has been proposed that the suppressive capacity of a Foxp3+ TIGIT- IL-6Rhi Treg population could be ‘disarmed’ in the presence of IL-6-associated inflammation, allowing for the activation of effector functions and tissue damage [15]. Foxp3+ Treg can also convert to Th17 upon exposure to IL-6 [16]. This is regulated in part by miR-125a, which reduces *IL6R* making Treg less sensitive to IL-6 and able to retain regulatory features [17]. Exposure of Teff cells to IL-6 is known to bolster their resistance to suppression by Tregs; Teff resistance has been previously established in T1D, MS, juvenile idiopathic arthritis (JIA), SLE and psoriasis [14,18–21]. STAT3 appears to play a central role in the resistance of Teff to Treg. Studies in MS demonstrated the ability to revert Teff resistance *in vitro* through the use of a STAT3 inhibitor [14]; more recently Ihantola *et al*. found Teff resistance was STAT3-dependent in T1D [20].

A recent study shows an influence of IL-6 on naïve T cell activation via TCR, which may have broad implications with respect to the activation and development of autoreactive T cells. Tu *et al*. demonstrate that TβR1 expression regulates T cell responsiveness in naïve T cells [22]. TGF-β blunts the response to TCR stimulation, enforcing a quiescent state. The response to TGF-β in naïve T cells is regulated through the expression of cell surface TβR1. Strong stimuli overcome the suppression of T cell activation by reducing TβR1 and allowing cells to become activated and mature. IL-6 blocks TβR1 upregulation, allowing for increased T cell activation, a diminished naïve T cell population and the potential to promote the activation of low affinity T cells; this may be a mechanism through which IL-6 could promote Teff resistance [22].

In the context of humoral immunity, IL-6 functions as a central link between T cell and B cell responses. IL-6 promotes the survival, expansion, and maturation of B cells and plasmablasts, in part by promoting the development of T follicular helper (Tfh) cells [5,23]. The activation of STAT3 by IL-6 and IL-21 enhances expression of the transcriptional repressor, Bcl-6, and promotes commitment to the Tfh lineage. Tfh cells localize to B cell follicles where they promote B cell proliferation and immunoglobulin class switching [24]. B cells are also an important source of IL-6. B cell-derived IL-6 drives a murine model of MS by supporting the development of Th17 cells in the central nervous system [25]. B cell-

derived IL-6 is required for spontaneous germinal center formation and development of murine lupus [26]. IL-6 produced by B cells promotes the development of Tfh cells [27].

The IL-6 pathway: Unique roles for classic, trans- and cluster signaling

As noted above IL-6 signals via three distinct mechanisms (Figure 2). Classic signaling is mediated by the membrane bound IL-6 receptor (mbIL-6R). IL-6 binds the mbIL-6R leading to recruitment of gp130, which then activates JAK1 and JAK2, leading to phosphorylation of the transcription factors, STAT1 and STAT3 [5]. Trans-signaling is mediated by the soluble IL-6 receptor (sIL-6R), instead of mbIL-6R. Here, IL-6 binds to sIL-6R then forms a complex with cell surface gp130, this allows IL-6 to act on cells that express gp130 but which lack mbIL-6R [28]. Notably gp130 is broadly expressed and soluble gp130 (sgp130) can act to block trans-signaling [29]. The expression of mbIL-6R and sIL-6R are central to the regulation of these signaling pathways. Two distinct mechanisms have been identified for the generation of sIL-6R: alternative splicing and shedding. In humans, a splice variant lacking the transmembrane domain leads to expression of sIL-6R [30]. Ectodomain shedding refers to proteolytic cleavage of the extracellular domain of IL-6R, which is tightly regulated and mediated by ADAMs (a disintegrin and metalloprotease). ADAM17 has been identified as the major protease involved in IL-6R shedding following TCR activation in human CD4 T cells [31].

Cluster signaling, a third form of IL-6 signaling, was described in 2017 by Heink *et al.* [16]. This IL-6 cluster signaling occurs in dendritic cells where IL-6 is complexed with the IL-6R in intracellular compartments before being transported to the membrane to activate gp130 in target cells. While sgp130 can interfere with IL-6 trans-signaling, it does not impact cluster signaling; this mode of IL-6 signaling contributes to the generation of Th17 cells via the induction of STAT3 and the upregulation of the IL-23R in the presence of TGF-β1 [8,32]. Importantly, cluster signaling induces faster and more robust activation of STAT3 compared to classic IL-6 signaling [16].

Both IL-6 trans-signaling and cluster signaling play more detrimental roles in adaptive immunity by regulating the differentiation of Th17 cells, suppressing Tregs and contributing to chronic inflammation [16,33,34]. This suggests that Th17 cell differentiation requires multiple IL-6 sources and signaling modes that function as a safeguard to minimize unwanted Th17 cell-dependent immunopathology [35]. IL-6 classic signaling suppresses the differentiation of Foxp3+ Tregs and plays a central role in the development of Tfh cells and germinal centers [5,34]. Blockade of IL-6 classic signaling, but not trans-signaling, alleviated multiorgan autoimmunity in a murine model of enhanced IL-6 expression in follicular B cells dependent on IL-6-driven Tfh [27].

The IL-6/IL-6R axis is dysregulated in autoimmunity

Significant differences in the expression of mbIL6R and sIL6R are found among individuals. Twin studies have demonstrated that up to 72% of these differences can be attributed to genetics with 51% linked to a single genetic variant the Asp358Ala (rs2228145) [36,37]. This genetic variant alters the amino acid in the ADAM17 cleavage site resulting in

increased shedding, increased sIL-6R in serum and decreased mbIL-6R levels on CD4 T cells [38,39]. Alterations in mbIL6R and sIL6R are associated with autoimmunity. The *IL6R,* Asp358Ala (rs2228145) genetic variant is associated with T1D and RA, where increased mbIL-6R expression could lead to higher IL-6 signaling capacity in CD4 effector T cells [39]. There is also a significant reduction in transcript and protein levels of ADAM17 in T cells from subjects with T1D, which correlate with expression of mbIL-6R and suggests a role for ADAM17 in the mechanism of altered IL-6 signaling in T1D [40]. How cluster signaling may be implicated in autoimmunity is still under investigation.

Targeting the IL-6 pathway has proven to be therapeutic in autoimmunity

Anti-IL-6R antibodies

The first approved drug to block the IL-6 signaling pathway in autoimmunity was a humanized anti-IL-6R monoclonal antibody, tocilizumab (TCZ) [41]. The FDA has approved the use of TCZ in the treatment of RA and JIA. In Japan, TCZ is approved for the treatment of Castleman's disease [1]. Tocilizumab blocks both the classic and trans-signaling pathways by preventing IL-6 from binding to mbIL-6R and sIL-6R [42]. The efficacy of TCZ in treating other autoimmune disease is being explored in ongoing clinical trials including those in systemic sclerosis [43], neuromyelitis optica [44] and new-onset T1D (clinicaltrials.gov NCT02293837). Most recently, a second anti-IL-6R antibody, sarilumab, which binds to the IL-6R with up to a 40-fold higher affinity than TCZ, was approved for the treatment of RA [45].

Anti-IL-6 antibodies

There is also a class of anti-IL-6 antibodies being developed for the treatment of autoimmune diseases. One of the first anti-IL-6 antibodies, siltuximab, functions by inhibiting IL-6 binding to the IL-6R and is approved for the treatment of Castleman's disease [46]. Treatment with sirukumab has improved symptoms in RA patients that previously failed anti-TNF therapy [47]. A third anti-IL-6 antibody, clazakizumab, improved musculoskeletal manifestations in patients with psoriatic arthritis [48]. Additionally, some of these therapies are also being tested in the setting of malignancy and transplantation [49,50].

JAK inhibitors

Janus kinase (JAK) family enzymes participate in signal transduction of multiple cytokines. Inhibitors of JAKs, Jakinibs, have been developed to for the treatment of inflammatory diseases and cancer. Tofacitinib is a JAK3 specific inhibitor that also inhibits JAK1 and JAK2 and thus has the potential to block IL-6 signaling. Tofacitinib is approved for RA and ulcerative colitis and is effective in a broad range of dermatological conditions including alopecia areata [51] and psoriasis [52]. There is ongoing development of additional Jakinibs including the JAK3-specific inhibitor, peficitinib, which has shown promise in RA [53].

In addition to improving treatment of autoimmunity, blockade of the IL-6 pathway has allowed us to develop a broader understanding of how IL-6 influences the lymphocyte population and its function *in vivo*. Treg and Th17 cells are altered with TCZ treatment in RA patients. An increase in the ratio of Treg to Th17 cells with therapy is a common finding

in these studies; this is predominantly due to an increase in Treg [54,55] though there is limited evidence of decreased Th17 cells [34]. Moreover, Treg function is improved with TCZ therapy in RA and correlates with clinical response, in part due to an increase in the frequency of functionally suppressive CD39+ Tregs [54,56]. Further, natural killer cells are also found to inversely correlate with DAS28 disease score after three months of TCZ treatment [57]. Anti-IL-6 therapies have not been available long enough for their impact to be known; limited studies of tofacitinib demonstrate increases in B cell counts but impaired plasmablast development [58,59]. These findings support the multiple roles played by IL-6 in defining the character of the CD4 T cell and B cell response in human health and disease.

Concluding Comments

Due to its pleiotropic nature, IL-6 has multiple roles in host defense and in human disease, from autoimmunity to cancer. Our understanding of how IL-6 influences the immune response continues to grow, exemplified by the recent discovery of IL-6 cluster signaling and its unique impact on T cell responses [35] alongside the many studies describing the immunologic consequences of IL-6R blockade in humans [33,56]. As the IL-6/IL-6R axis continues to be implicated in more autoimmune diseases, the need to better understand the dysregulation of the signaling pathways driving these diseases also grows. Ultimately, therapeutics targeting the IL-6/IL-6R axis may need to be further tailored to specific cell types or tissue compartments. An example of this is the development of a bispecific antibody against Il-6R and IL-17A, a novel therapeutic approach that could be used to target the Th17 lineage and its pathogenicity in autoimmunity [60]. Future investigation into the cell types, tissues and dysregulated signaling pathways involved in the IL-6/IL-6R axis will enable a more streamlined process of drug development and therapeutic selection.

Acknowledgements

This work was supported by the National Institutes of Health (Grant numbers: 1 DP3 DK104466 and 5 R01 AI132774). The authors wish to thank Anne Hocking for editing and proofing the manuscript.

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HIGHLIGHTS

1. IL-6 promotes development of Th17 and Tfh cells and suppresses induction of Treg.
2. IL-6 signals via three distinct mechanisms: classical, trans- and cluster signaling.
3. IL-6/IL-6R axis is dysregulated in autoimmunity.
4. Targeting the IL-6 pathway has proven to be therapeutic in autoimmunity.

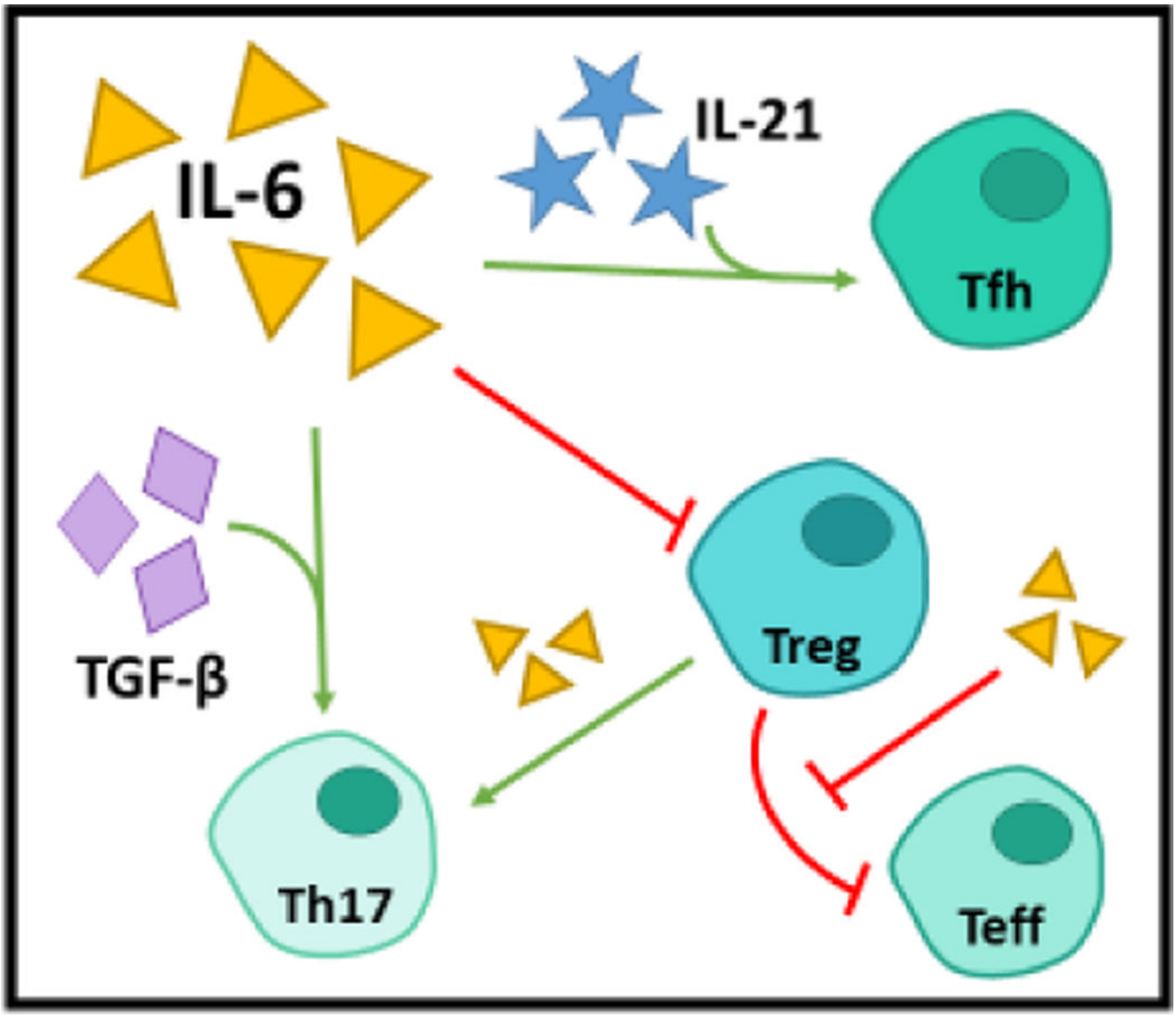

Figure 1. IL-6 is a proinflammatory modulator of T cells.

IL-6 contributes to autoimmunity by promoting Tfh, Th17, and Teff lineage and function and by inhibiting the suppressive capacity and induction of Tregs. In the presence of IL-21, IL-6 promotes commitment to the Tfh lineage, which is capable of stimulating B cell proliferation and class switching. In addition to bolstering Teff resistance to suppression by Tregs, IL-6 also promotes the conversion of Tregs to Th17 and may reduce Treg suppressive capacity. Lastly, in the presence of TGF-β, IL-6 enhances commitment and function of Th17 cells, a well-established pathogenic cell type in autoimmunity.

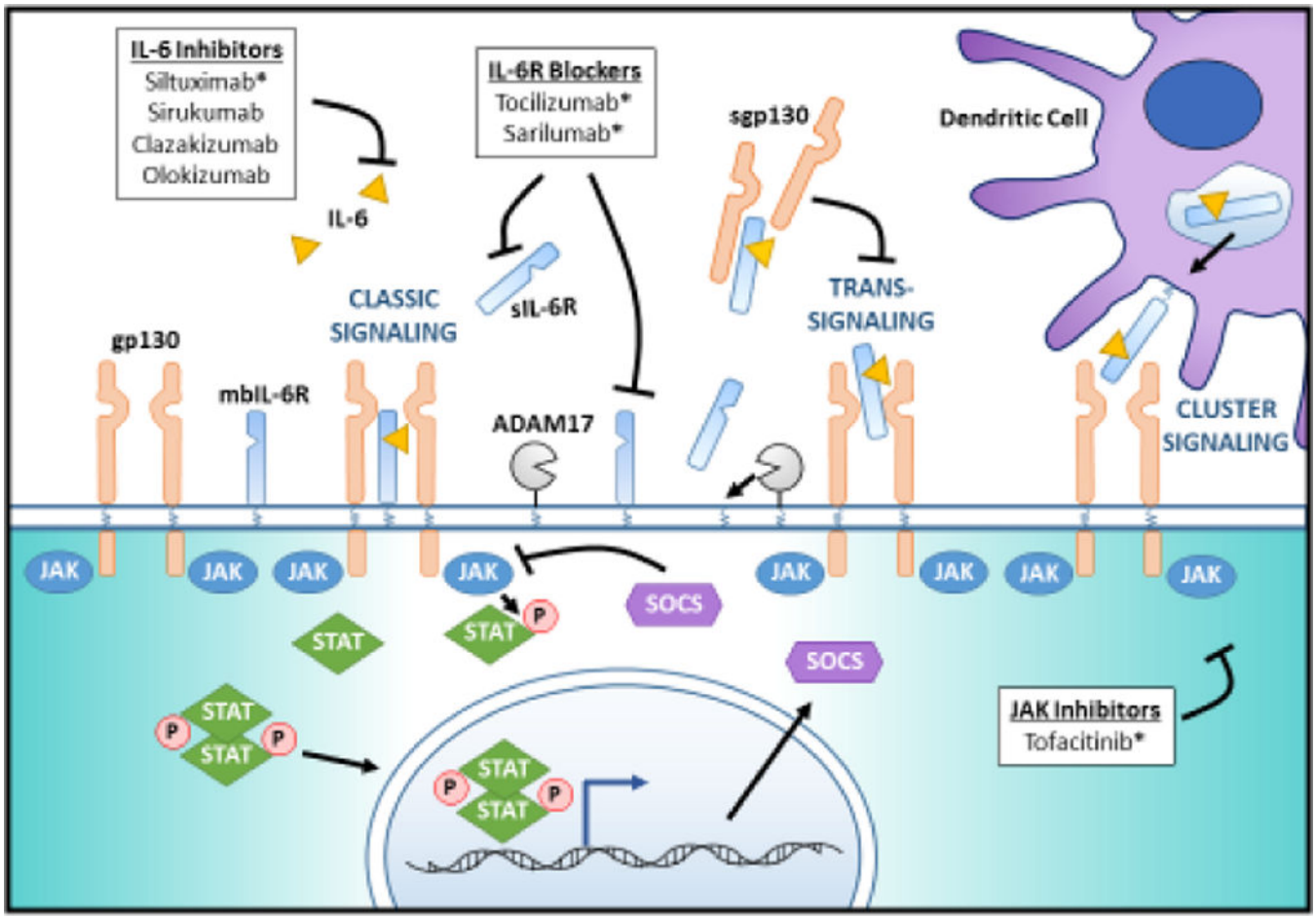

Figure 2. Signaling modes, JAK/STAT cascade and therapeutic targets.

IL-6 signals via three mechanisms: classic signaling mediated by the membrane bound IL-6 receptor (mbIL-6R), trans-signaling mediated by the soluble IL-6 receptor (sIL-6R) and cluster signaling in dendritic cells (DCs). In classic signaling, IL-6 binds the mbIL-6R leading to recruitment of gp130, which then activates JAK1 and JAK2, leading to phosphorylation of the transcription factors, STAT1 and STAT3. Activated STAT3 induces a negative-feedback molecule, suppressor of cytokine signaling (SOCS), SOCS1 and SOCS3. In trans-signaling, IL-6 binds extracellular sIL-6R before complexing with gp130 and initiating the JAK/STAT cascade. Trans-signaling is inhibited by extracellular sgp130, which can complex with sIL-6R and prevent it from binding to the membrane-bound gp130. Classic signaling and trans-signaling may be augmented by ADAM17, which cleaves mbIL-6R to generate sIL-6R. In cluster signaling, IL-6 is complexed with IL-6R within intracellular compartments in DCs before being transported to the membrane to activate gp130 in target cells. Current IL-6 targeting therapies inhibit either IL-6, the IL-6R, or JAK. IL-6 inhibitors include siltuximab, sirukumab, clazakizumab, and olokizumab. Siltuximab is approved for the treatment of Castleman's disease. Il-6R blocking drugs tocilizumab and sarilumab are both approved for the treatment of RA. Tofacitinib, a JAK inhibitor, is

approved for the treatment of RA and has a demonstrated therapeutic effect in ulcerative colitis, alopecia areata, and psoriasis. *indicates FDA approval for an autoimmune disease