

## Review Article



# Lessons From the Success and Failure of Targeted Drugs for Rheumatoid Arthritis: Perspectives for Effective Basic and Translational Research

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## OPEN ACCESS

Received: Jan 17, 2022

Revised: Feb 15, 2022

Accepted: Feb 16, 2022

Published online: Feb 22, 2022

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### Conflict of Interest

The authors declare no potential conflicts of interest.

## ABSTRACT

Rheumatoid arthritis (RA) is a representative autoimmune disease that is primarily characterized by persistent inflammation and progressive destruction of synovial joints. RA has a complex and heterogeneous pathophysiology, involving interactions among various immune and joint stromal cells and a diverse network of cytokines and intracellular signaling pathways. With improved understanding of RA, over the past decades, therapeutic strategies have become considerably advanced and now included targeted molecular therapies, such as tumor necrosis factor inhibitors, IL-6 blockers, B-cell depletion agents, as well as inhibitors of T-cell co-stimulation and Janus kinases. However, a considerable proportion of RA patients experience refractory disease and interrupted treatment owing to the associated risk of developing serious infections and cancers. In contrast, although IL-1 $\beta$ , IL-17A, and p38 $\alpha$  play significant roles in RA pathogenesis, several drugs targeting these factors have not been approved because of their low efficacy and severe adverse effects. In this review, we provide an overview of the working mechanism, advantages, and limitations of the currently available targeted drugs for RA. Additionally, we suggest potential mechanistic causes for clinically approved and failed drugs. Thus, this review provides perspectives on approaches for basic and translational studies that hold promise for identifying future next-generation therapeutics for RA.

**Keywords:** Rheumatoid arthritis; Targeted molecular therapies; Cytokines; Janus kinase

## INTRODUCTION

Rheumatoid arthritis (RA) is a common autoimmune disease that causes persistent inflammation, resulting in irreversible joint destruction, which ultimately leads to disability and mortality (1,2). Most evidence from immunological and bio-molecular studies points to an immune-mediated etiology associated with stromal tissue dysregulation, which together propagate chronic inflammation and joint damage in RA. Thus, RA is characterized by the complex process of disordered innate and adaptive immune responses, dysregulated cytokine and signal transduction networks, and disease-progressing semi-autonomous features of joint stromal synovial fibroblasts (3,4).

### Abbreviations

ADA, anti-drug Ab; APC, Ag-presenting cell; bDMARD, biologic disease-modifying anti-rheumatic drug; CIA, collagen-induced arthritis; CRP, C-reactive protein; DC, dendritic cell; EPO, erythropoietin; FDA, Food and Drug Administration; GIP, gastrointestinal perforations; IL-1Ra, IL-1 receptor antagonist; IL-36Ra, IL-36 receptor antagonist; IL-6R, IL-6 receptor; mIL-6R $\alpha$ , membrane-bound IL-6R $\alpha$ ; MK2, MAPKAP kinase 2; MKK3, MAPK kinase 3; MKK6, MAPK kinase 6; MTX, methotrexate; RA, rheumatoid arthritis; SCID, severe combined immunodeficiency; sIL-6R $\alpha$ , soluble form of IL-6R $\alpha$ ; TB, tuberculosis; TCZ, tocilizumab; TNFR1, TNF receptor 1; TPO, thrombopoietin; tsDMARD, targeted synthetic disease-modifying anti-rheumatic drug; TYK, tyrosine kinase.

### Author Contribution

Conceptualization: Kim M, Choe YH, Lee SI; Funding acquisition: Kim M, Lee SI; Writing - original draft: Kim M, Choe YH, Lee SI.

Over the past three decades, a comprehensive understanding of RA pathogenesis, by virtue of basic and translational research, and the consequent clinical availability of targeted agents, has led to a step-change in RA treatment (5). Currently, two types of clinically successful targeted drugs for RA exist: (1) injectable biologic disease-modifying anti-rheumatic drugs (bDMARDs), including TNF- $\alpha$  inhibitors, IL-6 blockers, B-cell depletion agents, and inhibitors of T-cell co-stimulation; (2) oral targeted synthetic DMARDs (tsDMARDs), including small molecules inhibiting the JAK pathway. Current therapies have led to substantial progress toward achieving disease remission and preventing joint deformity in patients with RA. Thus, RA is a notable example of successful immunologic and clinical attempts, based on tissue culture cells, animal models, and human translational studies, which have led to enormous therapeutic advances.

Despite this, at best, these drugs induce significant clinical improvement in less than two-thirds of patients, most of whom will undergo a relapse of the disease after drug withdrawal (1,6). Furthermore, current RA drugs are not curative, nor do they reverse joint destruction. Additionally, current targeted therapies can result in a considerable burden of adverse events, including serious infection and malignancy, which is a consequence of drug cessation (7,8). In contrast, biologic agents blocking IL-1 $\beta$ , IL-17A, and small molecule inhibitors of p38 $\alpha$  have exhibited disappointing therapeutic results and severe adverse effects in clinical trials, even though these targets have meaningful roles in RA pathogenesis. Collectively, these findings suggest that further basic and experimental research is required to explore additional therapeutic targets responsible for the complete resolution of inflammation while balancing efficacy and toxicity. An in-depth understanding and key lessons regarding successful and failed targeted agents may provide a novel effective direction for immunobiological research regarding feasible and desirable next-generation therapies for RA.

### TNF- $\alpha$

#### *Identification of TNF- $\alpha$*

TNF- $\alpha$  is a potent chemoattractant and inflammatory cytokine that is primarily produced as a transmembrane protein that gets cleaved by a TNF-converting enzyme, leading to the release of soluble TNF- $\alpha$  (9). TNF- $\alpha$  is predominantly produced by monocyte-derived macrophages; however, it is also produced by other cell types, including endothelial cells, cardiac myocytes, adipose tissue, fibroblasts, and neurons (10,11). Recently, by combining single-cell sequencing and mass cytometry, B cells and T cells have also been identified as major sources of TNF- $\alpha$  in the synovium of patients with RA (12). TNF- $\alpha$  has two receptor isoforms, namely, TNF receptor 1 (TNFR1) and TNFR2. TNFR1 is expressed on most nucleated cells, whereas the expression of TNFR2 is limited to immune cells, such as T cells and myeloid cells, and may be associated with the regulatory function of TNF- $\alpha$  (10).

#### *Role of TNF- $\alpha$ in RA*

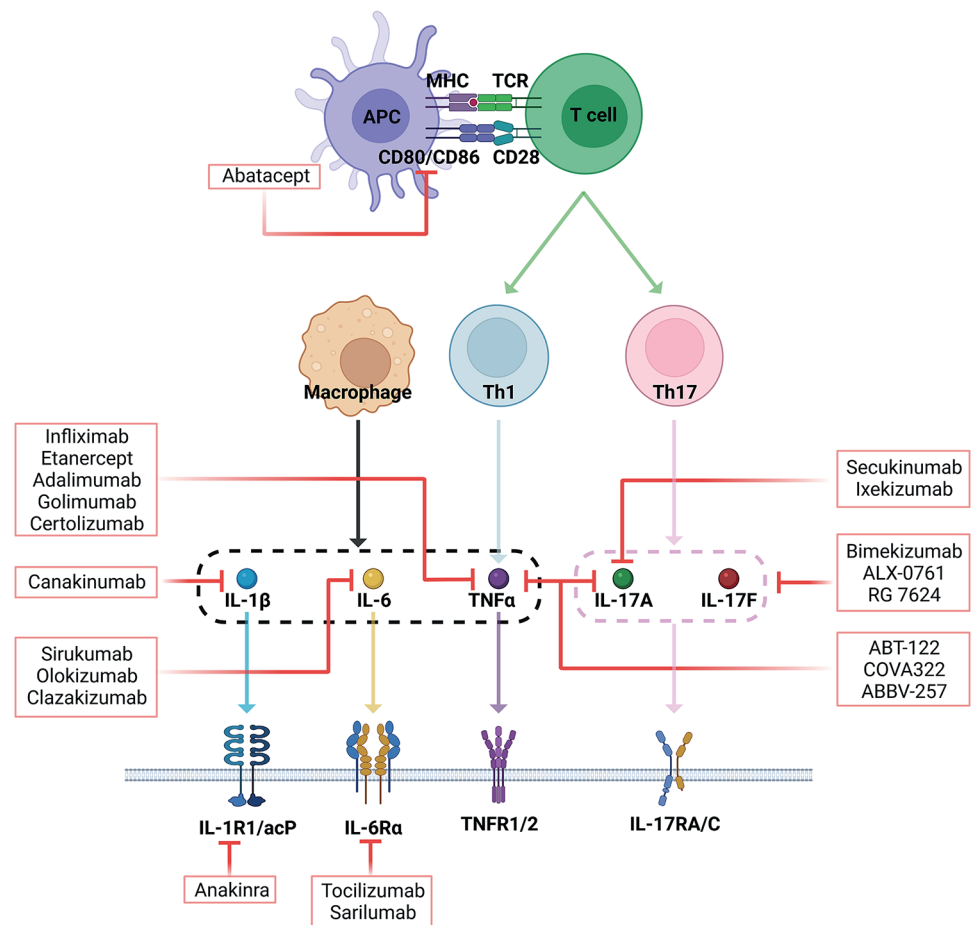
TNF- $\alpha$  is a key cytokine that has multipotent and central roles in RA pathogenesis by activating joint resident synovial fibroblasts to release various cytokines and chemokines, while also recruiting pro-inflammatory immune cells, including macrophages, monocytes, lymphocytes, and neutrophils (10,11). TNF- $\alpha$  also promotes osteoclast differentiation and activity, while inhibiting osteoblast differentiation and function (13). Furthermore, TNF- $\alpha$  suppresses Foxp3 production by Tregs and promotes the differentiation of Th1 and Th17 cells (14,15).

Indeed, several experimental animal studies have supported the crucial roles of TNF- $\alpha$  in RA. For instance, human TNF-overexpressing transgenic mice spontaneously develop

inflammatory arthritis characterized by joint inflammation and bone erosion, similar to the pathologic findings of human RA (16). Moreover, in collagen-induced arthritis (CIA) mice, another representative experimental model of RA, blockade of TNF- $\alpha$  efficiently attenuates joint inflammation and consequent destruction (17).

*Targeting of TNF- $\alpha$  in RA*

As TNF- $\alpha$  is a potent pro-inflammatory cytokine with a central role in RA pathophysiology, large-scale clinical trials have been conducted to develop several TNF- $\alpha$  inhibitors, including infliximab, which was first approved in 1999 (Fig. 1) (18). Infliximab is a chimeric monoclonal Ab comprising mouse heavy and light chain variable regions (Fab) combined with human heavy and light chain constant Fc regions (19). Infliximab binds to soluble and membrane-attached TNF- $\alpha$ , effectively inhibiting its binding to TNFR. Subsequently, it blocks Ab and complement-dependent responses in cells expressing TNFR (20).



**Figure 1.** Overview of inhibitors targeting cytokines and their specific receptors in RA treatment. Abatacept blocks CD80 and CD86 in the interface between APC and T cells. Inhibitors of TNF- $\alpha$ , such as infliximab, etanercept, adalimumab, golimumab, and certolizumab, specifically bind TNF- $\alpha$ . Inhibitors of IL-6, such as tocilizumab and sarilumab, prevent IL-6 from binding to its receptor (IL-6R $\alpha$ ). Sirukumab, olokizumab, and clazakizumab are anti-IL-6 monoclonal Abs that specifically bind IL-6. Secukinumab and ixekizumab are anti-IL-17A monoclonal Abs. ABT-122, COVA-322, and ABBV-257 are dual targeting Abs that block both IL-17A and TNF- $\alpha$ . Bimekizumab, ALX-0761, and RG-7624 target the combination of IL-17A/IL-17F. Anakinra and canakinumab exhibit inhibitory effects by directly binding IL- $\beta$  and IL-1 $\beta$  receptor 1 (IL-1 $\beta$ R1), respectively. The red lines indicate where the inhibitors block cytokines or their receptors.

Etanercept, another TNF- $\alpha$  inhibitor, contains a human soluble TNFR2 conjugated to the Fc portion of human IgG1. Etanercept binds to soluble TNF- $\alpha$  and TNF- $\beta$ , not membrane-attached TNF- $\alpha$ , thus interfering with TNF- $\alpha$  binding to its natural receptors on pathologic cells.

Adalimumab is a fully humanized anti-TNF- $\alpha$  monoclonal Ab that binds to both soluble and transmembrane TNF- $\alpha$ . Similarly, golimumab is a fully-humanized IgG1 kappa monoclonal Ab that binds to the soluble and transmembrane bioactive forms of TNF- $\alpha$  (21). Still further, certolizumab is a humanized TNF- $\alpha$  monoclonal Ab Fab fragment linked to polyethylene glycol (22); compared with other TNF- $\alpha$  inhibitors, certolizumab elicits minimal adverse effects. Moreover, considering that it removes the Fc portion required for active transport across the placenta, it is theoretically safer for use during pregnancy (23).

#### *Clinical success and limitations of targeting TNF- $\alpha$ in RA*

As bDMARDs, the introduction of targeted therapy against TNF- $\alpha$  has markedly improved RA therapy and shifted the primary aim of treatment strategies from symptom control to achieving and maintaining RA remission. Although TNF- $\alpha$  inhibitors have achieved significant clinical success, several limitations have also arisen. First, the use of TNF- $\alpha$  inhibitors is associated with an increased risk of infection, especially tuberculosis (TB). TNF- $\alpha$  plays a vital role in the formation of granulomas, which are critical for protection of the host from TB. Thus, inhibition of TNF- $\alpha$  prevents granuloma formation and promotes the dissemination of TB infection (24). To overcome this issue, physicians can perform a latent TB detection test and administer prophylactic TB medication. Second, TNF- $\alpha$  inhibitor use is also associated with an increased potential risk of malignancy, such as lymphoma and non-melanoma skin cancer. Although a recent meta-analysis has shown that treatment with TNF- $\alpha$  inhibitors does not significantly increase the risk of developing malignancies, TNF- $\alpha$  exhibits selective cytotoxicity and can induce necrosis of tumor cells. Therefore, the risk of malignancy should be considered when prescribing prolonged use of TNF- $\alpha$  inhibitors (25,26). Third, a progressive decrease in TNF- $\alpha$  inhibitor efficiency has been reported. This is believed to be associated with development of anti-drug Abs (ADAs), the prevalence of which ranges from 5% to 20% in RA patients using TNF- $\alpha$  inhibitors (27). To circumvent this issue, TNF- $\alpha$  inhibitors are regularly administered in combination with methotrexate (MTX) to inhibit ADA production (28).

## IL-6

### *Identification of IL-6*

IL-6 was first discovered in 1986 as a secreted component that stimulates Ig production and is a multifunctional cytokine with a pivotal role in immunological control, hematopoiesis, and inflammation (29). Most immune cells and stromal cells produce IL-6, including macrophages, monocytes, T cells, B cells, osteoblasts, fibroblasts, and endothelial cells (30). The biological effects of IL-6 are mediated by a fully functional IL-6 receptor (IL-6R), which comprises two subunits: a type I cytokine receptor subunit, IL-6R $\alpha$  (also called CD126), and a common signal-transducing-receptor subunit, gp130 (also called CD130) (31). Fully functional IL-6R (IL-6R $\alpha$ /gp130) is primarily expressed in lymphocytes, myelocytes, megakaryocytes, and hepatocytes, whereas gp130 is expressed in a wide range of cells (31,32).

IL-6R exhibits three distinct signaling modes: classical signaling, trans-signaling, and trans-presentation signaling. First, classical signaling is mediated by the membrane-bound IL-6R $\alpha$  (mIL-6R $\alpha$ ) subunit and gp130. IL-6 binds to mIL-6R, leading to the homo-dimerization of gp130 and activation of an intracellular signal transduction pathway (32). Second, trans-

signaling is induced by the soluble form of IL-6R $\alpha$  (sIL-6R $\alpha$ ). IL-6 binds sIL-6R $\alpha$  to form the IL-6-s-IL6R $\alpha$  complex, which binds to, and activates signal transduction in cells expressing only gp130, such as synovial fibroblasts and endothelial cells (33). Third, trans-presentation involves secreted IL-6 binding to mIL-6R $\alpha$  expressed on dendritic cells (DCs); this complex then interacts with gp130 on CD4 T cells. This type of contact is necessary for Th17 cell priming (34).

#### *Role of IL-6 in RA*

IL-6 has multifunctional roles in RA pathogenesis. In an animal experiment, IL-6 deficiency protects against CIA development, whereas neutralizing IL-6 with an Ab improves the CIA clinical score (35). Moreover, IL-6 and sIL-6R $\alpha$  are expressed in the serum and synovial fluid of RA patients, the levels of which correlate with disease activity and joint damage (36,37). Specifically, recent single-cell transcriptomics revealed that IL-6 is produced by T cells, B cells, and synovial fibroblasts within the RA synovium (12). IL-6 promotes Th17 differentiation, which is critical for inducing joint inflammation and destruction through the JAK/STAT pathway (38). Therefore, IL-6 production exacerbates an imbalance in Th17 cells and Tregs. Furthermore, IL-6 is essential for B-cell differentiation into memory B cells and plasma cells, via affinity maturation and class switching. These memory B cells and plasma cells then produce autoantibodies in the RA synovium (39). In addition, IL-6 upregulates osteoclastogenesis, which causes bone erosion in RA patients, and VEGF expression, which promotes angiogenesis, as well as the recruitment of inflammatory and immune cells into the joints (18,40).

#### *Targeting of IL-6 in RA*

IL-6 has been multi-directionally involved in the pathogenesis of RA and has become a target for RA therapeutics. Tocilizumab (TCZ) is a recombinant humanized anti-IL-6R $\alpha$  monoclonal Ab approved for RA treatment (**Fig. 1**). TCZ inhibits the binding of IL-6 to mIL-6R $\alpha$  and sIL-6R $\alpha$ , thereby preventing the IL-6-mediated inflammatory signaling cascade (41). Thus, TCZ suppresses disease activity and progressive bone erosion in RA patients (42).

Sarilumab, another recombinant humanized anti-IL-6R $\alpha$  monoclonal Ab, has also been approved by the Food and Drug Administration (FDA) for RA treatment. Sarilumab shows high efficacy in RA patients with moderate-to-severe activity who do not respond to conventional DMARDs (43). Meanwhile, several other biologics, including sirukumab, olokizumab, and clazakizumab, that target IL-6, not IL-6R, are currently undergoing clinical trials as RA therapeutics (**Fig. 1**) (44).

#### *Clinical success and limitation of targeting IL-6 in RA*

Although TCZ was developed after TNF inhibitors, which had already dominated the market, it has exhibited considerable success as a biologic. The tremendous success of IL-6 targeting agents for RA treatment may be due to several factors. First, the efficacy of TCZ supersedes that of adalimumab in RA patients (45). Second, TCZ monotherapy shows comparable clinical efficacy to the combined therapy of TCZ and MTX, whereas anti-TNF- $\alpha$  monotherapy demonstrates lower clinical efficacy than anti-TNF- $\alpha$  combined with MTX. This advantage of TCZ as a monotherapy is highly attractive as one-third of RA patients develop various adverse events to MTX, including nausea, vomiting, skin rash, or aggravation of hepatitis and complicated lung diseases. Third, TCZ has low immunogenicity and thus does not cause significant ADA production (46). The immunogenicity of ADAs can alter the drug's pharmacokinetics, pharmacodynamics, or other biological activities, thereby impacting the

safety and efficacy in RA patients receiving biologics treatment (46). Finally, TCZ inhibits pathological IL-6 signaling, which is associated with C-reactive protein (CRP) production. Thus, TCZ rapidly decreases CRP levels. High CRP levels in RA patients are associated with severe disease activity, whereas a rapid decrease in CRP eventually improves clinical outcomes (47).

Despite the clinical success of IL-6 targeting therapy, several considerations must be made. IL-6-mediated signaling is also required to mount protective immune responses; therefore, blockade of IL-6 increases the risk of infections (48). Moreover, TCZ administration is associated with a significantly increased incidence rate of lower gastrointestinal perforations (GIP), such as diverticulitis, compared to other conventional synthetic DMARDs and bDMARDs, such as TNF- $\alpha$  inhibitors abatacept, and rituximab (48). Therefore, TCZ treatment should be prescribed with caution to RA patients so as to minimize these risks.

### CD80/CD86, Co-stimulatory molecule

#### *Identification and role of CD80/CD86 and CTLA-4*

Immune synapses that are formed between Ag-presenting cells (APCs) and T cells are required to initiate immune cascades. T cells require three signals for effector functions and differentiation, namely, primary, secondary, and cytokine signaling. The primary signal comprises Ag recognition by TCRs. APCs express MHC class II molecules on their surface, which present Ags to the TCR on T cells. Secondary co-stimulation-mediated signaling then occurs with CD80/CD86, which is upregulated on the surface of APCs and binds to CD28 on T cells. In fact, CD28 signaling acts synergistically with the TCR complex to activate the transcription factors NFAT, NF- $\kappa$ B, and AP-1. Activated T cells differentiate into various subsets, such as Th1, Th2, Th17, Tfh, and Treg, based on the cytokines in their surroundings (49). Meanwhile, CTLA-4 binds CD80/CD86 with a 100-fold higher affinity than CD28 and functions as an inhibitory signal. As such, CTLA4 is a powerful negative regulator of immune responses and is highly expressed on Tregs (50).

#### *Targeting of CD80/CD86 in RA*

As the APC-T-cell-B-cell immune cascade is implicated in the pathogenesis of RA, a new class of treatment was developed to inhibit co-stimulation by binding to CD80/CD86. Abatacept is a dimeric fusion protein made up of the CTLA-4 extracellular domain and an IgG Fc region (CTLA4-Ig) (51). As such, abatacept inhibits the co-stimulatory signal required for T-cell activation and the subsequent production of autoantibodies, which are direct drivers of disease activity (Fig. 1) (51). Furthermore, the Fc region of abatacept can bind CD16/CD32, known as Fc $\gamma$ RIII and Fc $\gamma$ RII, to reduce Fc-mediated processes, complement-dependent cytotoxicity, and Ab-dependent cellular cytotoxicity (50). Indeed, several clinical studies have reported that abatacept exhibits anti-inflammatory effects and radiographic improvement in the MTX-refractory population. Meanwhile, combined abatacept and DMARD therapy also has valuable effects on disease activity in patients with an inadequate response to TNF- $\alpha$  inhibitors (52-54).

#### *Clinical success and limitation of targeting CD80/CD86 in RA*

The clinical success of abatacept is likely due to two major factors. First, inhibition of the upstream immune synapse, including the APC-T-cell-B-cell axis, by abatacept can minimize compensatory pathway activity by inhibiting various downstream cytokines. In this way, abatacept also reduces autoantibody production (55). Second, abatacept administration is associated with a lower incidence of serious infections in patients with RA, compared to other biologics. The reason is hypothesized that the CD28 and CD80/CD86 interaction, a

therapeutic target for abatacept, is higher in activated T cells than in naive T cells. Hence, with the ever increasing number of elderly patients being diagnosed with RA, abatacept is an appropriate treatment option as infection is an important consideration when selecting drugs for elderly patients (56).

Despite these advantages, select considerations must be made when administering abatacept. Some clinicians may be hesitant to choose abatacept for RA patients, as it is slower to reduce disease activity compared to that with other biologics (57). Moreover, abatacept can cross the placenta and therefore should be discontinued at least three months before preparing for pregnancy (58).

### IL-17A

#### *Identification of IL-17A*

IL-17A was the first member of the IL-17 cytokine family to be identified and defined. This family now includes IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F (59). IL-17A binds to IL-17RA and induces recruitment of IL-17RC to form a heterodimeric receptor complex (60). IL-17A plays a pivotal role in host defense against extracellular bacterial and fungal infections through neutrophil migration at the infection site (61).

#### *Role of IL-17A in RA*

The importance of IL-17A in the pathogenesis of RA was determined by identifying the increased production of IL-17A in the synovial tissue of RA patients (62,63). IL-17A exhibits diverse functions in RA, including NF- $\kappa$ B activation and IL-6 production in synovial fibroblasts, augmentation of osteoclastogenesis, as well as enhanced recruitment and activation of neutrophils, macrophages, and B cells (64,65). In the CIA model, administration of IL-17A in joints promotes arthritis with symptoms similar to those observed in RA patients (66). In contrast, inflammatory arthritis is significantly suppressed in IL-17- or IL-17R-deficient mice. Similarly, administration of IL-17A neutralizing Ab reduces the development and progression of arthritis (67,68). Furthermore, the discovery of Th17 cells, an IL-17A-producing specific CD4 T-cell subset, reinforced the pathogenic roles of IL-17 in RA (69).

#### *Limited clinical success of targeting IL-17 in RA*

In a phase I clinical trial, secukinumab and ixekizumab, which are fully human monoclonal IL-17A Abs, showed positive clinical responses (**Fig. 1**) (70,71). However, secukinumab has not successfully improved clinical outcomes in two phase II trials conducted in RA patients (72,73). In fact, secukinumab exhibited lower efficacy than abatacept in a phase III clinical trial (74,75). Thus, despite the promising data from experimental models and phase II clinical trials, the clinical efficacy of IL-17A inhibitors in RA has proven insufficient.

Several potential mechanistic causes may account for the limited clinical success exhibited by targeting IL-17 in RA. First, IL-17A inhibition alone is insufficient to disrupt the inflammatory cascade. IL-17A functions synergistically with other inflammatory cytokines, including TNF- $\alpha$ , IL-1 $\beta$ , and IL-6; thus, neutralization of only IL-17A does not inhibit the pro-inflammatory effects of TNF- $\alpha$ , IL-1 $\beta$ , IL-6 or initiation of chronic inflammatory cascades (76). Nevertheless, IL-17A and IL-17F can synergize with TNF- $\alpha$ ; thus, administration of dual neutralizing Abs, such as ABT-122, COVA-322, and ABBV-257 (target the combination of IL-17A and TNF- $\alpha$ ) or bimekizumab, ALX-0761, and RG-7624 (target IL-17A/IL-17F), may prove more effective than administration of IL-17A mono-blocking Abs (**Fig. 1**). Second, IL-17A may have meaningful roles only in the early phase of RA, not in the established phase. We

previously observed an increased abundance of Th17 cells during early, or before, disease onset compared to the disease progression phase. Moreover, IL-17A positive Th17 cells convert the IFN- $\gamma$  positive CD4 T cells in the CIA mice (unpublished data). Accordingly, it may be interesting that IL-17A blockade may serve as an effective preventive strategy for pre-RA patients, before arthritis onset. Third, in RA patients, IL-17A expression is heterogeneous, with not all patients having high IL-17A levels or Th17 cell populations (77). Fourth, IL-17A inhibitors do not only block pathologic Th17 but also regulatory Th17. In patients with RA, IL-10-producing regulatory Th17 cells express IL-17 receptors; thus, IL-17A inhibitors may also affect IL-10-producing non-pathological Th17 cells (78).

## IL-1 $\beta$

### *Identification of IL-1 $\beta$*

The IL-1 family comprises 11 members, including IL-1 $\alpha$ , IL-1 $\beta$ , IL-18, IL-33, IL-37, IL-38, IL-36 $\alpha$ , IL-36 $\beta$ , IL-36 $\gamma$ , IL-1 receptor antagonist (IL-1Ra), and IL-36 receptor antagonist (IL-36Ra). Among them, IL-1 $\beta$  is the most frequently studied cytokine in several inflammatory diseases, including RA, gout, systemic-onset juvenile idiopathic arthritis, adult-onset Still's disease, and osteoarthritis (79). IL-1 $\beta$  exhibits pro-inflammatory activities by binding to IL-1R1, forming a heterotrimeric complex with co-receptor IL-1R3 and triggering recruitment of MYD88 and the subsequent kinase cascade (80).

### *Role of IL-1 $\beta$ in RA*

Several animal studies have found that intra-articular injection, or increased expression of IL-1 $\beta$ , mediates infiltration of leukocytes and subsequent degradation of cartilage, resulting in a severe and aggressive arthritis phenotype, including human RA (81-83). Similarly, the presence of IL-1 $\beta$ , and its relevance in arthritis progression, has also been clearly demonstrated in RA patients (12,84). Based on this cumulative evidence, the primary role of IL-1 in RA pathogenesis is believed to involve innate, rather than acquired, immune responses (79). That is, the IL-1 $\beta$  produced by macrophages and monocytes promotes joint destruction by induction of osteoclastogenesis and cartilage degradation (80,85).

### *Limited clinical success of targeting IL-1 $\beta$ in RA*

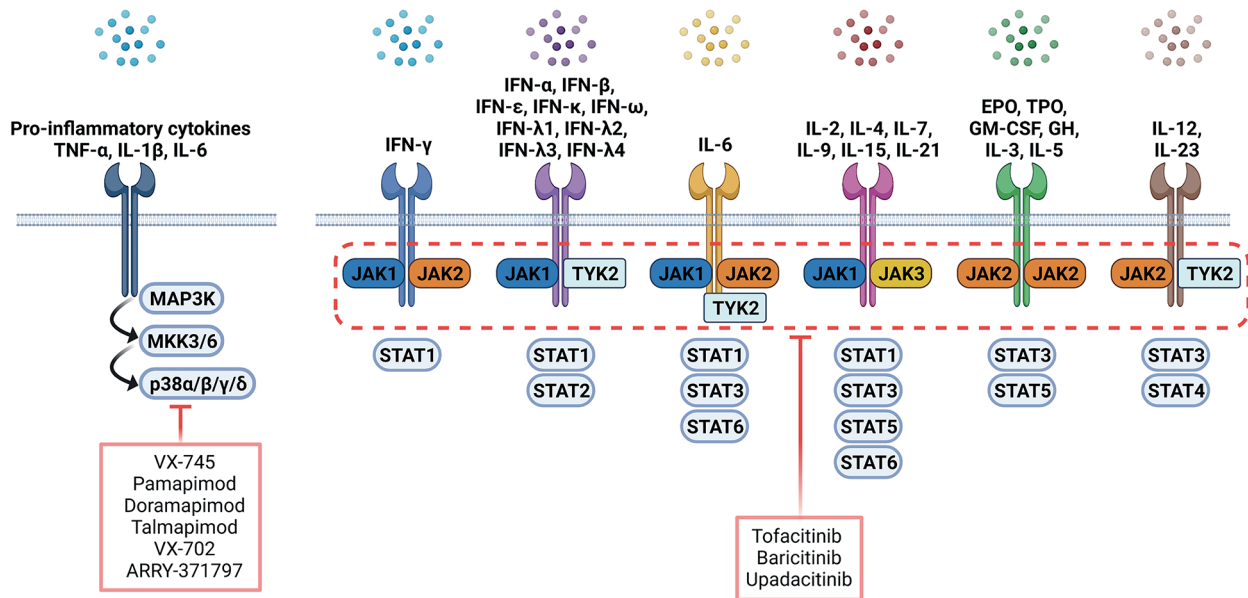
Anakinra (recombinant IL-1 receptor antagonist) and canakinumab (anti-IL-1 $\beta$  Ab) have been evaluated for their therapeutic efficacy in RA (Fig. 1) and have demonstrated responses that are less potent than those of anti-TNF agents (86,87). In fact, combined therapy of anakinra and methotrexate or etanercept also failed to offer any clinical advantages, yet increased the risk of associated infection (88). Moreover, administration of anakinra also reportedly causes erythema, itchiness, and discomfort at the injection site in some patients. Indeed, adverse injection site reactions were the most notable event resulting in the premature withdrawal of subjects from various clinical trials (89,90). These limited clinical responses and associated adverse events have prompted doubts regarding whether targeting IL-1 $\beta$  in RA is an effective strategy. Specifically, the short half-life (4–6 hours) and inconvenience of daily administration make anakinra a less favored choice for patients and clinicians in RA treatment (91).

## p38

### *Identification of p38*

MAPKs consist of 3 major families: ERK, JNK, and p38. ERK and JNK are important for cellular proliferation and differentiation and extracellular matrix regulation (92,93). p38 exists in four isoforms ( $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ ) that are widely expressed in not only various immune





**Figure 2.** Overview of small molecule inhibitors targeting the p38 MAPK pathway and JAK/STAT pathway in RA treatment. Each cytokine receptor recruits and activates a specific combination in MAPK and JAK/STAT cascades. Tofacitinib is a pan-JAK inhibitor, selective for JAK3 and JAK1 with minor activity for JAK2 and TYK2. Baricitinib is selective for JAK1 and JAK2 and less selective for JAK3 and TYK2.

cells but also stromal cells (94). p38 is activated by various pro-inflammatory cytokines, including IL-1 $\beta$ , IL-6, and TNF- $\alpha$  (95) and is mediated by two upstream kinases, MAPK kinase 3 (MKK3) and MAPK kinase 6 (MKK6). In turn, phosphorylated p38 triggers signaling cascades associated with the expression of various pro-inflammatory molecules (Fig. 2) (96). As such, p38 MAPK has attracted attention as a potential target for autoimmune diseases.

#### Role of p38 in RA

The roles of p38 were first recognized in the investigation of LPS-stimulated monocytes, in which p38 was found to be associated with the synthesis of pro-inflammatory cytokines (97). Among the four p38 isoforms,  $\alpha$  is thought to be the most important in mediating inflammation, with several studies supporting a pathogenic function of p38 $\alpha$  in arthritis. Early *in vitro* studies demonstrated that the production of IL-1, IL-6, and TNF, key mediators of RA, is regulated by p38 $\alpha$  (97-99). Meanwhile, deficiency of major upstream kinases of p38 $\alpha$ , MKK3 or MKK6, ameliorates arthritis severity and cartilage destruction in K/BxN serum-transferred mice (100,101). Moreover, in CIA mice, deficiency of MAPKAP kinase 2 (MK2), the p38 $\alpha$  substrate, also contributes to reduced production of IL-1 and TNF as well as arthritis severity (102). p38 $\alpha$  is also, reportedly, associated with collagen- or TNF- $\alpha$ -driven arthritis (103). Meanwhile in RA patients, p38 $\alpha$  and  $\gamma$  predominate the synovium in the synovial tissue, in particular within the lining layer and vessels (94). Taken together, these evidences suggest a critical role for p38 $\alpha$  and its signaling cascades in RA pathogenesis.

#### Limited clinical success of targeting of p38 MAPK in RA

After demonstrating the therapeutic effect of p38 inhibitors in animal models of RA (104,105), numerous p38 inhibitors, including VX-745 (106), pamapimod (107,108), doramapimod (BRIB 796) (109), talmapimod (SCIO-469) (110), VX-702 (111), and ARRY-371797 (NCT00729209), were evaluated in clinical trials for RA treatment (Fig. 2). However, no significant improvement was reported disease severity or outcome. These disappointing clinical results have raised questions regarding the potential associated causes of the failure.

First, one of the major limitations of p38 inhibitors is their low efficacy and poor safety profile. Together with their limited efficacy in RA treatment, p38 inhibitors are associated with high rates of hepatotoxicity—talmapimod (110), pamapimod (107), and doramapimod (112), which is the primary cause of patient withdrawal from the clinical trials. Meanwhile, infection, skin disorders, and dizziness are also commonly reported adverse effects of p38 MAPK inhibitors (107,110).

Second, it is unclear whether the  $\alpha$  isoform of p38 is the most effective target for RA treatment. Although p38 $\alpha$  is the best characterized isoform, and its pathological role has been well demonstrated *in vitro* (97-99) and *in vivo* (100-103), recent data suggest an anti-inflammatory effect of p38 $\alpha$ . For instance, IL-10 production in macrophages requires p38 $\alpha$  regulation (113). Indeed, evidence also exists regarding the importance of other p38 isoforms, namely,  $\beta$  and  $\gamma$ . In particular, it has been suggested that p38 $\beta$  regulates the synthesis of endothelial chemokines and exhibits pro-inflammatory effects (114). Meanwhile, phosphorylated p38 $\gamma$  is also highly expressed in the RA synovium, suggesting a correlation between this isoform and RA pathogenesis (94).

Third, the compensatory effect on other kinases caused by blocking downstream p38 must also be considered (115). MKK3, MKK6, and TAK1, which regulate p38 upstream, can be activated by p38 inhibition, leading to the regulation of NF- $\kappa$ B or redirecting signaling cascades (100,116). This suggests that targeting these upstream kinases of p38 may be an attractive alternative for RA treatment.

## JAK/STAT PATHWAY

### Identification of JAK/STAT

The JAK/STAT pathway comprises intracellular tyrosine kinases (TYKs) that have a pivotal role in the signaling pathways associated with immune responses. When cytokines, growth factors, chemokines, and colony-stimulating factors bind to their cognate receptors, receptors dimerize (**Fig. 2**) causing cross-phosphorylation by JAK (117). Phosphorylation of receptor-associated tyrosine residues offers docking sites for STAT proteins. Phosphorylated STAT forms a dimer, translocate to the nucleus, and regulates gene expression (117). Humans have 4 different JAKs: JAK1, JAK2, JAK3, TYK2, and 7 STATs, including STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6 (118).

### Role and targeting of JAK/STAT in RA

Cytokines, such as IFN- $\gamma$ , IL-6, IL-12, IL-17A, and GM-CSF play a crucial role in RA. These cytokines regulate gene expression via the JAK/STAT pathway in immune cells as well as synovial fibroblasts (117). Hence, the JAK/STAT pathway is strongly involved in RA pathophysiology and is a target of RA treatment. The essential cytokines impacted by the JAK/STAT pathway include the interferon family, IL-2, IL-4, IL-6, IL-7, IL 10, IL-12, IL-23, GM-CSF, G-CSF, erythropoietin (EPO), thrombopoietin (TPO), leptin, and growth hormone (**Fig. 2**). JAKs and STATs combine to generate complex multimers that affect the immune system and hematopoiesis in a variety of biochemical and physiological ways (119). In fact, JAK deficiencies, or genetic gain of functions of other JAKs, can cause several diseases. Specifically, genetic mutations in JAK1 can lead to lymphoid malignancy, while genetic mutations in JAK2 can lead to myeloproliferative disease (120). JAK3 congenital deficiency

is strongly associated with severe combined immunodeficiency (SCID), whereas STAT3 congenital deficiency is linked with hyper-IgE syndrome (120).

JAK inhibitors are small molecules and the newest class of tsDMARDs for RA treatment. Tofacitinib was the first targeted synthetic, reversible, and non-selective JAK inhibitor that was FDA approved for the treatment of RA. The structure of tofacitinib and most JAK inhibitors, mimics ATP and competitively binds to the ATP-binding site in the TYK domain (119). Tofacitinib is a pan-JAK inhibitor that has a high degree of selectivity for JAK3 and JAK1; however, it exhibits minimal activity for JAK2 and TYK2 (119). The phase III trial of tofacitinib demonstrated a significantly higher clinical response and limited joint damage progression in patients administered tofacitinib compared to MTX monotherapy (121). Meanwhile, administration of tofacitinib with MTX exhibited similar efficacy to adalimumab with MTX (122).

Baricitinib is more selective for JAK2 and JAK1 compared to JAK3 and TYK2. Baricitinib also successfully passed four phase III clinical trials during the approval process. In the RA-BEGIN trial, baricitinib monotherapy exhibited superior efficacy compared to MTX monotherapy (123). Meanwhile, in the RA-BEAM trial, baricitinib demonstrated superior clinical efficiency and reduced radiographic progression compared to adalimumab (124).

Upadacitinib is a second-generation JAK inhibitor with increased selectivity for JAK1 over JAK2, JAK3, and TYK2 (125). In all five pivotal clinical trials, upadacitinib showed significantly higher rates of remission and low disease activity compared to the placebo, methotrexate, or adalimumab (126).

### Clinical success of targeting JAK/STAT in RA

JAK inhibitors are a rapidly-growing therapy option for RA therapy. There are several potential reasons for this success. First, they provide a targeted oral medication with efficacy comparable to that of TNF inhibitors (122,124). In particular, their oral formulations make them a convenient and appealing treatment option for patients with RA. Second, JAK inhibitors block upstream signal transduction, unlike the p38 MAPK inhibitor, which is a small molecule with high associated clinical failure (119). Moreover, it is stable against the activation of compensatory pathways, which can occur when downstream signaling is blocked. Third, JAK inhibitors modulate dysregulated metabolism by inducing oxidative phosphorylation while reducing glycolysis, thus offering opportunities for restoring synovial homeostasis by direct targeting of aggressive RA synovial fibroblasts (127). Finally, the essential cytokines for RA pathophysiology operate through various JAK/STAT pathways; thus, JAK inhibitors simultaneously interfere with signaling pathways across multiple cytokine axes.

However, several adverse events can occur by inhibition of multiple JAK/STAT pathways. The representative risk is hematopoietic toxicity, which is presumed to be caused by JAK2 inhibition.

## CONCLUSION

In this review, we identified that selection of the proper therapeutic target is crucial for the clinical success of targeted drugs in RA, such as cytokines with multipotent and pleiotropic activity and kinases in upstream immune synapse or upstream signal transduction

**Table 1.** Overview of the potential reasons for clinical success or clinical failure of targeted RA therapies

Clinical approved	Target	Potential reasons and lessens
Success	TNF- $\alpha$	<ul style="list-style-type: none"> <li>✓ First approved bDMARD for RA</li> <li>✓ Multipotent and central role of TNF-<math>\alpha</math> in RA pathophysiology</li> </ul>
	IL-6	<ul style="list-style-type: none"> <li>✓ Pleiotropic activity of IL-6 in RA pathogenesis</li> <li>✓ Low incidence of anti-drug Ab</li> <li>✓ Rapid reduction of inflammation</li> </ul>
	CD80/CD86	<ul style="list-style-type: none"> <li>✓ Blockade of upstream immune-synapse in the inflammatory cascade</li> <li>✓ Relatively less susceptible to infection by mainly suppressing activated T cells rather than naive T cells</li> </ul>
	JAK/STAT	<ul style="list-style-type: none"> <li>✓ Blockade of upstream signal transduction</li> <li>✓ Blockade of signaling pathways across multiple cytokine axes simultaneously</li> <li>✓ Oral formulation; convenient to take medicines</li> </ul>
Failure	IL-1 $\beta$	<ul style="list-style-type: none"> <li>✓ Short half-life and need for daily injection</li> <li>✓ Higher risk of infection compared to efficacy</li> </ul>
	IL-17A	<ul style="list-style-type: none"> <li>✓ Disease heterogeneity of RA with variable expression of IL-17A</li> <li>✓ Meaningful roles of IL-17A only in the early phase of RA, but not in the established phase</li> <li>✓ Blocks not only pathologic Th17 but also regulatory Th17</li> </ul>
	MAPK p38 $\alpha$	<ul style="list-style-type: none"> <li>✓ Compensatory activation of upstream kinase pathways upon p38<math>\alpha</math></li> <li>✓ Blocks not only pro-inflammatory p38<math>\alpha</math> but also anti-inflammatory p38<math>\alpha</math></li> <li>✓ Pro-inflammatory roles of additional isoforms of p38</li> </ul>

pathways (**Table 1**). Moreover, the success of targeted drugs may be the result of several potential factors, including convenience of treatment, balancing efficacy and safety, and cost. Additionally, as we have suggested regarding JAK inhibitors, direct suppression of aggressive synovial fibroblasts may also contribute to the success of RA drugs. In particular, the immunopathologic contribution of tumor-like synovial fibroblasts to arthritis relapse following discontinuation of drugs appears highly significant in RA; the stromal origin of these cells may render them resistant to current immune-targeted therapies. Thus, we predict that combining an immune-targeted agent with a synovial fibroblast-directed therapy might increase the rate of RA remission without increasing the risk of infection and cancer development. Collectively, the integration of proper targets based on lessons learned from clinically approved or failed drugs, as well as tandem targeting of pathologically relevant immune and stromal cell subsets, is critical to designing effective RA therapies. This approach may facilitate new research directions to achieve curative measures without additional side effects and recurrences for RA patients.

## ACKNOWLEDGEMENTS

This study was supported by a grant from National Research Foundation of Korea (NRF-2020R1C1C1007944) and from the Korea Health Technology R&D project through the Korea Health Industry Development Institute (KHIDI) funded by the Korean Ministry of Health and Welfare (grant number: HI14C1277). We would like to thank Editage ([www.editage.co.kr](http://www.editage.co.kr)) for English language editing.

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