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Review

# Novel Immunotherapeutic Avenues for Rheumatoid Arthritis

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**Rheumatoid arthritis (RA) is the most common inflammatory rheumatic disease. It leads to irreversible joint damage, physical handicap, and reduced life expectancy. The past two decades have seen considerable therapeutic advances with the development of biologic treatments to block proinflammatory cytokines or modulate lymphocyte function, followed by the development of small molecules to target intracellular signaling. Nevertheless, only a minority of patients can achieve disease remission, especially long term, warranting further investigation into newer therapeutic options. Targeting single proinflammatory pathways may not be sufficient, as suggested by variable results with T helper (Th)-17-related cytokine blockade. Multilevel information from 'omics' techniques along with data from mechanistic studies might facilitate the identification of pivotal checkpoints in RA disease pathogenesis and the subsequent development of new effective treatments.**

## Rheumatoid Arthritis: A Model for Treating Chronic Inflammatory Diseases

RA is a chronic inflammatory disease of unknown etiology that is characterized by systemic and synovial inflammation. The pathogenesis of RA is a multistep process that may initially start outside the joints. The process first involves the activation of innate immune cells [neutrophils, resident macrophages, and dendritic cells (DCs)] by one or more environmental factors, with activation of the inflammatory cascade, as well as processing and presentation of one or more autoantigens to cells of the adaptive immune system [1]. **Citrullination** (see Glossary) and **carbamylation** of proteins can generate **T antigens** that trigger persistent immune activation in susceptible subjects [2]. In some populations, the association of RA with polymorphisms of genes encoding proteins involved in T cell activation, such as *HLA-DRB1*, *PTNP22*, *CTLA4*, and *STAT4*, supports the role of genetics in the perpetuation of the immune response [1].

The hallmark of the persistent immune response, with involvement of the B cell compartment, is the production of **rheumatoid factor** (RF) and **anticitrullinated peptide antibodies** (ACPAs) that can precede disease onset by several years in some, but not all, patients [3]. In a later phase, immune cells interact with endothelial and stromal cells to infiltrate the joints (and sometimes other organs) with patterns that can vary from diffuse cellular infiltrates to more organized lymphoid aggregates, to structures that histologically resemble secondary lymphoid organs. **Regulatory T cells** (Tregs), although over-represented in the affected joints and synovial fluid, cannot limit the persistent immune activation and inflammation in the joint, where cell–cell interactions and local production of proinflammatory cytokines, chemokines, antibodies, lipid mediators, and metalloproteinases occurs. This inflammatory microenvironment is characterized by low oxygen tension and active neoangiogenesis (*ex novo* formation of blood vessels) [4].

### Trends

Current standard therapeutic options for RA involve targeting proinflammatory cytokines [such as tumor necrosis factor (TNF)-α and interleukin (IL)-6] or intracellular signaling pathways, depleting B cells, and controlling T cell activation.

Several novel specific inhibitors of Janus kinase (JAK) isoforms and new biologics targeting IL-6 or IL-6 receptor (IL-6R) may enrich the therapeutic armamentarium in the near future.

Initial targeting of most Th17 cytokines may have been deceptive, but blockade of cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), have provided good clinical results. However, further testing is required.

*In vivo* expansion of regulatory T cells by different means is being tested in clinical trials, although this approach remains challenging and controversial.

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Hence, inflammation and angiogenesis cooperate to promote and support the proliferation of fibroblast-like synoviocytes (FLSs) that form the pannus, a tumor-like tissue invading cartilage and bone. Concomitantly, **osteoclasts** are activated by inflammatory cytokines and directly by ACPA [5] In this inflammatory milieu, immune cells, such as T lymphocytes and macrophages, undergo profound metabolic changes, with a shift toward anaerobic glucose metabolism and the accumulation of metabolic intermediates that allow cell activation, proliferation, and differentiation toward an effector phenotype.

All these events, if uncontrolled, lead to irreversible joint damage and loss of function (Figure 1, Key Figure). An improved understanding of the chronic inflammatory process in RA has led to the generation of a novel class of therapeutics called biologic disease-modifying antirheumatic drugs (bDMARDS, Box 1), which have revolutionized the treatment of RA over the past two decades. Understanding the pivotal role of proinflammatory cytokine networks in the rheumatoid synovium has led to the identification of tumor necrosis factor ∝ (TNF-∝) and interleukin 6 (IL-6) as relevant therapeutic targets. RA was the first disease for which anti-TNF biologics were used. In this sense, RA served as model for targeted treatments in other inflammatory diseases characterized by localized tissue damage, such as psoriasis or Crohn's disease, and for which anti-TNF treatments have also proved effective. Targeted immunotherapies for RA have been enriched by other biologics, developed to modulate lymphocyte function (Box 1) and, recently, by small molecules that target intracellular signaling [synthetic (s)DMARDs, Box 1]. These considerable therapeutic advances have radically changed the prognosis of patients with RA, and remission is now an achievable objective. Nevertheless, only a few patients achieve longstanding remission with treatment [6]. Persistent remission off therapy is even rarer. Moreover, we lack solid biomarkers to stratify patients for treatment, and the choice and prioritization of therapeutics is based only on expert opinion. Hence, further dissection of the cellular and molecular pathways in RA is needed, both for identifying novel avenues for treatment and for better characterization of patients at the molecular level to guide therapeutic choices.

In this review, we focus on therapeutics registered at ClinicalTrials.gov between January 2011 and October 2015 and which continue their clinical development. Moreover, we describe

## Box 1. Treatment and Outcomes in RA

RA is characterized by a chronic inflammatory process that, if uncontrolled, leads to permanent joint damage, physical handicap, and increased mortality. Hence, controlling inflammation is the main therapeutic goal of RA treatment to modify these disease outcomes. Disease activity reflects systemic and articular inflammation, and is measured, in both clinical trials and clinical practice, by composite indexes, such as the **Disease Activity Score 28 joints** (DAS28), Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI). Different cut-off points define high, moderate, and low disease activity and remission for each score. Conversely, American College of Rheumatology (ACR) response rates are used to define clinical response only in clinical trials. Disease outcomes are mainly measured in clinical trials to assess the efficacy of new treatments or therapeutic strategies. Several imaging scores measure joint damage both by MRI (RAMRIS score) and standard radiography (modified-Sharp and Larsen score). Questionnaires, such as the **Health Assessment Questionnaire** (HAQ), are used to measure the level of handicap.

The cornerstone of RA treatment is based on specific immunosuppressants, such as methotrexate (MTX), leflunomide or sulfasalazine, called synthetic DMARDS (sDMARDs). Current therapeutic strategies aim for remission and involve aggressive treatment of early disease, prompt adaptation of sDMARD treatment based on disease activity, and therapeutic escalation with the addition of other sDMARDs, or the introduction of biologic DMARDs (bDMARDs) if low disease activity or remission is not achieved [90]. bDMARDs are targeted treatments that block the actions of specific cytokines or immune regulators. TNF inhibitors (anti-TNF) were the first approved bDMARDs, but the therapeutic armamentarium for RA has enriched over the years with the T cell activation inhibitor abatacept; with rituximab, a B cell-depleting monoclonal antibody (mAb); and tocilizumab (TCZ), an anti-IL-6 receptor mAb. A novel class of small-molecule immunosuppressants, called targeted synthetic DMARDs (tsDMARDs), modeled to interact with specific defined molecules, mainly intracellular kinases, has recently enriched the pool of available therapeutics.

## Glossary

**Anti-citrullinated peptides antibodies (ACPA):** autoantibodies in the serum of patients with RA; highly specific for RA.
**Carbamylation:** post-translational modification transforming an amino group into a carbamyl group.
**CD19 and CD20:** B cell-specific regulatory cell surface receptors.
**Citrullination:** post-translational modification consisting in the deimination of an arginine residue into citrulline.
**Collagen-induced arthritis (CIA):** widely used model of experimental arthritis, induced by type II collagen immunization with complete Freund's adjuvant.
**Disease Activity Score 28 joints (DAS28):** composite score measuring RA disease activity that considers: the number of tender and swollen joints, C-reactive protein concentrations or erythrocyte sedimentation rate, as well as the patient's evaluation of their general health state. It is a continuous measure of disease activity with cut-off points that define remission, low-, moderate- and high-disease activity. Other disease activity scores are Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI).
**Health assessment questionnaire (HAQ):** evaluates a patient's physical function: dressing, rising, eating, walking, hygiene, reach, grip, and other activities
**K/BxN mice:** mice expressing both the T cell receptor transgene KRN and the MHC class II molecule A(g7); they develop spontaneous arthritis,
**K/BxN scurfy mice:** K/BxN mice carrying the *scurfy* loss-of-function mutation of the *FOXP3* gene. Due to the absence of thymus-derived Tregs, K/BxN scurfy mice exhibit earlier onset and more aggressive progression of arthritis compared with K/BxN mice.
**K/BxN serum transfer model:** serum from K/BxN mice causes arthritis, due to autoantibodies recognizing glucose-6-phosphate isomerase.
**Nanobodies:** therapeutic proteins derived from heavy-chain-only antibodies, a form of antibody that lacks light-chain; they occur naturally in the Camelidae family (camels). Nanobodies are highly stable proteins