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Mechanism-Based Drug Repurposing Strategies for Rheumatoid Arthritis

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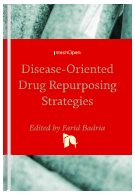

FROM THE EDITED VOLUME

Disease-Oriented Drug Repurposing Strategies [Working Title]

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Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder characterized by persistent synovial inflammation, progressive joint destruction, and systemic complications. Despite advances in disease-modifying antirheumatic drugs (DMARDs), therapeutic heterogeneity, incomplete response, safety concerns, and high treatment costs continue to limit optimal disease control. This chapter presents a mechanism-based narrative review of drug repurposing strategies in RA, emphasizing the pharmacological rationale for repositioning approved or clinically investigated agents based on shared pathogenic mechanisms. Key inflammatory pathways, including cytokine signaling, JAK–STAT, NF-κB, MAPK, and immunometabolic networks, are critically examined as therapeutic targets. The chapter integrates evidence from pharmacological studies, network pharmacology, molecular docking, multi-omics approaches, and translational clinical research to evaluate repurposing candidates originating from oncology, metabolic, cardiovascular, anti-infective, and neuropharmacological indications. Clinically supported therapies are distinguished from exploratory candidates supported primarily by preclinical or computational evidence. Major translational barriers, including inconsistent clinical validation, safety concerns, economic constraints, and regulatory challenges, are discussed. The importance of biomarker-guided patient stratification, precision rheumatology, and integrated multi-omics approaches is highlighted to improve translational success. Although mechanism-based repurposing offers considerable promise in RA, robust experimental and clinical validation remains essential before computational predictions can be translated into meaningful therapeutic outcomes.

Keywords

rheumatoid arthritis | drug repurposing | immunopharmacology | inflammatory signaling pathways | JAK–STAT pathway

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterized by persistent synovitis, progressive cartilage and bone destruction, and substantial functional disability. Beyond articular manifestations, RA is associated with systemic complications involving the cardiovascular, pulmonary, skeletal, and neuropsychological systems, which contribute significantly to morbidity, reduced quality of life, and healthcare burden. Recent global burden estimates indicate that RA continues to impose a major public health challenge, with approximately 11.88 million cases reported among the working-age population in 2021, accompanied by considerable disability-adjusted life-year loss and pronounced regional disparities in disease burden [ ]. Despite major therapeutic advances, long-term disease control remains difficult for a considerable proportion of patients.

Current RA management relies primarily on disease-modifying antirheumatic drugs (DMARDs), including conventional synthetic agents, biologics, and targeted synthetic therapies. Methotrexate remains the anchor conventional DMARD and is widely recommended as first-line treatment; however, many patients fail to achieve sustained remission or adequate disease control with methotrexate monotherapy. Escalation to biologic DMARDs or Janus kinase (JAK) inhibitors has improved outcomes for many individuals, yet treatment responses remain heterogeneous, and difficult-to-treat RA continues to represent a recognized clinical challenge. Moreover, the high cost of biologics, concerns regarding long-term safety, immunosuppression-related adverse effects, and unequal accessibility across healthcare settings limit therapeutic optimization for many patients [,].

These limitations have intensified interest in drug repurposing as an alternative strategy for accelerating therapeutic innovation in RA. Drug repurposing, also referred to as drug repositioning, involves identifying new therapeutic applications for approved or clinically investigated compounds outside their original indication. Because repurposed agents already possess established pharmacokinetic, toxicological, and safety data, this strategy can reduce development time, financial burden, and translational risk compared with conventional de novo drug discovery [,].

Historically, some repurposed therapies emerged through empirical or serendipitous observations, where beneficial anti-inflammatory effects were recognized unexpectedly during clinical use for unrelated diseases. However, contemporary RA research increasingly emphasizes mechanism-based repurposing, a rational and target-oriented approach in which candidate drugs are selected according to shared molecular pathways, immune signaling mechanisms, or pathogenic networks between diseases. In RA, this strategy is particularly relevant because key inflammatory pathways, including cytokine-mediated signaling, nuclear factor kappa B (NF-κB) activation, oxidative stress pathways, and intracellular kinase cascades such as JAK–STAT and mitogen-activated protein kinase (MAPK), overlap substantially with mechanisms implicated in oncology, metabolic disorders, cardiovascular disease, and chronic inflammatory conditions [,]. Such mechanistic convergence provides opportunities to identify non-rheumatologic drugs capable of modulating synovial inflammation, immune-cell activation, fibroblast dysfunction, and tissue destruction.

Mechanism-based repurposing is further strengthened by advances in computational pharmacology, systems biology, transcriptomics, molecular docking, and network medicine. These approaches enable systematic mapping of drug–target–pathway interactions and improve the prioritization of compounds with biologically plausible anti-rheumatic effects before costly clinical investigation. Existing examples, including the successful transition of methotrexate from oncology to RA treatment, demonstrate how mechanistic understanding can transform therapeutic positioning and improve disease management [,].

This chapter presents a mechanism-based perspective on drug repurposing strategies in RA. It first examines the immunopathological basis of RA and the signaling pathways that sustain synovial inflammation. It then discusses the pharmacological rationale for repurposing, key molecular targets, and major repurposed drug classes investigated for RA management. Computational and systems-based approaches supporting candidate identification are subsequently reviewed, followed by available clinical and translational evidence. Finally, current challenges, regulatory considerations, and future directions for mechanism-guided drug repurposing in RA are discussed.