Advances in Pharmacology and Therapeutics Journal

Shahid Sadoughi University of Medical Sciences, Yazd, Iran

SHAHID SADOUGHI UNIVERSITY OF MEDICAL SCIENCES

Letter to Editor

Future Immunologic and Nanotechnology-Based Therapeutic Strategies in Rheumatoid Arthritis

Running Title: Immunologic and Nanotech Therapies in Rheumatoid Arthritis

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ARTICLEINFO

Received: 02/15/2026
Accepted: 06/10/2026

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Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent synovial inflammation, progressive cartilage destruction, and irreversible joint damage. Although conventional disease-modifying antirheumatic drugs (DMARDs), biologic agents, and targeted synthetic therapies such as Janus kinase (JAK) inhibitors have substantially improved disease outcomes, a significant proportion of patients fail to achieve sustained remission or develop treatment-related adverse effects (1). These limitations underscore the need for innovative therapeutic strategies that offer greater specificity, reduced systemic toxicity, and long-term immune regulation.

Keywords: Arthritis rheumatoid, Immunotherapy, Nanomedicine, Exosomes, Drug delivery systems.

Citation: Tahoori M.T. Future Immunologic and Nanotechnology-Based Therapeutic Strategies in Rheumatoid Arthritis. Adv Pharmacol Ther J. 2025;5(4): 229-232.

Antigen-Specific Immunotherapy and Cellular Tolerance Approaches

Antigen-specific immunotherapy represents a shift from broad immunosuppression toward restoration of immune tolerance. Therapeutic vaccines based on disease-relevant autoantigens, such as collagen-derived peptides, are designed to selectively expand regulatory T cells (Tregs) while suppressing pathogenic T helper 17 (Th17) responses (2). Preclinical studies have demonstrated that these vaccines can rebalance immune responses and attenuate inflammatory cascades in experimental models of RA.

Tolerogenic dendritic cells (tolDCs) provide a complementary cellular approach to immune reprogramming. By presenting autoantigens in a non-inflammatory context, tolDCs inhibit autoreactive T-cell activation and promote antigen-specific tolerance. Early-phase clinical trials indicate that tolDC-based therapies are feasible and well tolerated, supporting their potential role as disease-modifying interventions in RA (3).

Refined Cytokine and Intracellular Signaling Inhibition

Advances in biologic therapy have led to increasingly selective cytokine inhibition. Monoclonal antibodies targeting interleukin-6 (IL-6), as well as dual inhibitors of interleukin-17A and interleukin-17F, demonstrate improved precision compared with earlier biologics (4). In addition, blockade of the granulocyte–macrophage colony-stimulating factor (GM-CSF) pathway has shown promise due to its central role in myeloid cell activation and synovial inflammation (5).

At the intracellular level, selective JAK1 inhibitors and Bruton's tyrosine kinase (BTK) inhibitors aim to preserve therapeutic efficacy while minimizing off-target immunosuppression (6). These approaches reflect a broader transition toward precision immunomodulation in RA.

Exosome-Based Immunomodulatory Therapies

Exosomes derived from mesenchymal stromal cells (MSCs) or immune cells have emerged as biologically active nanovesicles capable of delivering regulatory molecules to inflamed tissues. MSC-derived exosomes contain microRNAs, proteins, and lipids that suppress pro-inflammatory cytokine production, enhance Treg activity, and reprogram macrophages toward anti-inflammatory phenotypes (7). Experimental evidence suggests that exosome-based therapies can effectively modulate immune responses in autoimmune arthritis models.

Importantly, engineered exosomes enable controlled cargo loading and tissue targeting, offering a promising cell-free alternative to conventional cell therapies (8).

Nanoparticle-Mediated Targeted Drug Delivery

Nanotechnology has introduced innovative platforms for targeted drug delivery in RA. Polymeric nanoparticles, liposomes, and lipid-based carriers can be engineered to preferentially accumulate in inflamed synovial tissue, thereby improving therapeutic efficacy and reducing systemic toxicity (9). Stimuli-responsive nanoparticles that release drugs in response to acidic pH or oxidative stress further enhance site-specific delivery.

Encapsulation of methotrexate, biologics, or small

  DOI: https://doi.org/10.18502/aptj.v5i4.21763

interfering RNAs (siRNAs) within nanoparticles has demonstrated enhanced modulation of inflammatory pathways, such as NF-κB and JAK/STAT signaling, in preclinical studies (10, 11).

Targeting Fibroblast-Like Synoviocytes

Fibroblast-like synoviocytes (FLS) play a central role in sustaining chronic inflammation and joint destruction in RA. Therapeutic strategies targeting cadherin-11, fibroblast activation protein (FAP), or integrin-mediated interactions aim to disrupt immune–stromal crosstalk and limit synovial invasiveness (12). Combining FLS-targeted therapies with immunologic agents may improve the durability of remission.

Future Perspectives

The integration of antigen-specific immunotherapy, selective cytokine and kinase inhibition, exosome-based delivery systems, and nanotechnology-enabled targeting represents a promising direction for RA treatment. Future clinical success will depend on biomarker-driven patient stratification, synovial tissue profiling, and advanced imaging to assess drug distribution and immune modulation (13). Collectively, these emerging strategies have the potential to redefine RA management by combining precision, safety, and long-term disease control.

Conclusion

Emerging advances in immunology and nanotechnology are transforming the therapeutic landscape of rheumatoid arthritis. Antigen-specific immunotherapies, tolerogenic cellular approaches, selective cytokine and kinase inhibitors, exosome-based therapies, and nanoparticle-mediated drug delivery systems offer promising opportunities to improve treatment precision and long-term disease control. Although many of these strategies remain in preclinical or early clinical development, their integration into personalized treatment frameworks may help overcome the limitations of current therapies. Continued translational research and well-designed clinical studies are required to establish their safety, efficacy, and clinical applicability in routine rheumatoid arthritis management.

Table1: Emerging Immunologic and Nanotechnology-Based Strategies in Rheumatoid Arthritis

Therapeutic Approach	Mechanism of Action	Representative Example(s)	Stage of Development	Potential Clinical Impact
Antigen-specific vaccines	Induce tolerance by expanding Tregs and suppressing autoreactive Th17 cells.	Collagen peptide vaccine (CEL-4000)	Preclinical–early clinical	May restore long-term immune balance without global immunosuppression
Tolerogenic dendritic cells (tolDCs)	Present autoantigens in a non-inflammatory context to inhibit autoreactive T cells	Citrullinated peptide-loaded tolDCs	Early clinical trials	Personalized tolerance induction: potential disease-modifying therapy
Selective cytokine blockade	Neutralize pro-inflammatory cytokines driving synovitis	Olokizumab (IL-6), Bimekizumab (IL-17A/F), Mavrilimumab (GM-CSF)	Phase II–III clinical	Greater precision, reduced systemic toxicity compared to earlier biologics
Kinase inhibitors	Target intracellular signaling pathways critical for immune activation	Filgotinib (JAK1), Fenebrutinib (BTK)	Approved/Phase II	Pathway-specific inhibition with improved safety profile
Exosome-based therapy	Deliver immunoregulatory miRNAs and proteins to the inflamed synovium	MSC-derived exosomes, engineered exosomes	Preclinical	Cell-free therapy; natural nanocarriers for immune recalibration
Nanoparticle drug delivery	Enhance joint-specific accumulation and stimuli-responsive release	Methotrexate-loaded liposomes, siRNA nanoparticles	Preclinical–translational	Improved efficacy, reduced systemic toxicity, precision-guided delivery
Fibroblast-like synoviocyte targeting	Disrupt stromal–immune crosstalk sustaining chronic inflammation	Cadherin-11 antagonists, FAP-targeted therapies	Preclinical	May prevent pannus formation and joint destruction
Tolerogenic dendritic cells (tolDCs)	Combine tolerance induction with smart delivery and stromal targeting	Hybrid exosome–nanoparticle systems	Conceptual/early translational	Potential to achieve durable remission and disease modification

Acknowledgments: The author would like to express sincere appreciation to the researchers and clinicians whose contributions have advanced the understanding of immunologic and nanotechnology-based therapies for rheumatoid arthritis. Their work has provided the scientific foundation for the concepts discussed in this article.

Conflict of Interest: The author declares that there is no conflict of interest regarding the publication of this manuscript.

Funding: This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethical Considerations: This article is a narrative scientific communication based exclusively on previously published literature and does not involve human participants, animals, patient data, or clinical interventions. Therefore, ethical approval and informed consent were not required.

Author Contributions: Mohammad Taher Tahoori independently developed the concept of this article, reviewed the relevant literature, prepared the manuscript, and approved the final version for publication.

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  DOI: https://doi.org/10.18502/aptj.v5i4.21763