

Review

Bridging Pathogenesis and Precision Therapy: Immunoengineering Advancements in Rheumatoid Arthritis Management

Dheeraj Makkar * and Jonathan Morris

Emory University Hospital, 1364 Clifton Rd. NE, Atlanta, GA 30322, USA; jonathan.morris@emory.edu

* Correspondence: dmakka2@emory.edu

Abstract

Background: Rheumatoid arthritis (RA) is a persistent autoimmune condition defined by widespread synovial tissue inflammation and structural joint deterioration, with an estimated global prevalence between 0.5% and 3%. The disease predominantly targets synovial joints, resulting in progressive functional impairment when therapeutic intervention is delayed or inadequate. **Objective:** This review aims to comprehensively examine the contributing risk factors, underlying pathophysiological processes, and recently developed immunoengineering-based therapeutic strategies applicable to the clinical management of rheumatoid arthritis. **Methods:** A structured review of peer-reviewed literature was undertaken through PubMed, utilizing a targeted search strategy incorporating the terms ‘rheumatoid arthritis’ and ‘immunoengineering.’ Filters were applied to restrict results to English-language publications from peer-reviewed sources. The review emphasized studies investigating genetic susceptibility, environmental determinants, immune cell behaviour, and novel therapeutic advances in RA management. **Results:** Multiple interdependent risk factors underpin RA development, most notably genetic variants including HLA-DRb1 alleles, alongside demographic influences such as biological sex and advancing age, as well as obesity and pathogenic microbial exposure. These factors collectively initiate a self-amplifying inflammatory process characterized by protein citrullination and the subsequent generation of anti-citrullinated protein antibodies (ACPAs) and rheumatoid factor (RF). The ensuing immune dysregulation—driven principally by monocyte and T-lymphocyte infiltration—propagates synovial inflammation and progressively destroys cartilaginous and bony structures. **Conclusions:** While considerable progress has been achieved in RA pharmacotherapy, existing treatments remain constrained by systemic side effects and incomplete therapeutic responses. Emerging immunoengineering strategies offer a targeted approach to modulating the molecular and immunological milieu of affected joints, providing improved therapeutic precision. Continued investigation in this area is anticipated to yield novel clinical pathways capable of substantially enhancing patient outcomes in rheumatoid arthritis care.



Academic Editor: Bruce M. Rothschild

Received: 15 December 2025

Revised: 18 May 2026

Accepted: 26 May 2026

Published: 15 June 2026

Copyright: © 2026 by the authors.

Licensee MDPI, Basel, Switzerland.

This article is an open access article distributed under the terms and conditions of the [Creative Commons Attribution \(CC BY\)](https://creativecommons.org/licenses/by/4.0/) license.

Keywords: rheumatoid arthritis; immunoengineering; pharmacotherapy; synovial; anti-citrullinated protein

1. Introduction

Rheumatoid arthritis (RA) is a complex autoimmune disorder defined by persistent inflammation of the synovial membrane and incremental destruction of joint architecture,

affecting an estimated 0.5 to 3% of individuals worldwide. Notwithstanding advances in treatment options, a substantial proportion of patients continue to experience refractory pain, diminished physical function, and irreversible joint damage, placing increasing demands on long-term healthcare systems [1].

Contemporary treatment regimens—comprising both conventional and targeted disease-modifying agents—have meaningfully improved disease control; however, their utility is frequently constrained by systemic toxicity, the requirement for ongoing administration, and variable or waning clinical efficacy. These shortcomings highlight the imperative for more targeted, durable treatment modalities [2].

Immunoengineering represents an evolving therapeutic paradigm designed to meet these unmet clinical needs through targeted manipulation of the synovial immune microenvironment [3]. Platforms including nanoparticle-based drug delivery systems, cell-derived therapies, and biomaterial scaffolds are engineered to improve treatment specificity and confine therapeutic activity to sites of pathology [4]. By acting upon pivotal disease mechanisms—including immune cell polarization and cytokine network dysregulation—these innovations open a translational pathway toward more effective, individualized RA management [5].

2. Methods

2.1. Study Design

This work was carried out as a structured narrative review with the objective of synthesizing current understanding of RA pathobiology alongside advances in immunoengineering-based therapeutics. Given the diversity of available evidence—encompassing experimental, translational, and early-phase clinical data—quantitative meta-analysis was deemed unsuitable. A predefined literature search strategy was employed to ensure systematic coverage of relevant publications while enabling thematic, concept-driven synthesis.

2.2. Literature Search Strategy

A focused literature search was conducted using PubMed/MEDLINE as the primary database. Articles published between January 2010 and March 2026 were considered, encompassing both established foundational knowledge and recent developments. Boolean combinations of the following search terms were used: rheumatoid arthritis, pathogenesis, immunoengineering, nanotechnology, mesenchymal stem cells, exosomes, biomaterials, and precision medicine. Reference lists of selected articles were additionally screened to identify studies not retrieved through the primary search.

2.3. Eligibility Criteria

Studies were considered eligible if they were published in peer-reviewed journals, available in English, and addressed RA pathogenesis, immune regulation, or immunoengineering-based therapeutic interventions across preclinical, translational, or clinical settings. Studies were excluded if full-text access was unavailable, if they were published solely as conference abstracts, if they lacked mechanistic or translational relevance, or if they represented duplicate or overlapping data.

2.4. Study Selection and Data Extraction

The initial search identified approximately 1200 records. Following deduplication, around 1000 titles and abstracts were reviewed for relevance, from which approximately 300 articles were retrieved for full-text assessment. A total of 92 studies met the inclusion criteria based on their relevance, methodological rigour, and contribution to the review's objectives. Data were extracted qualitatively, focusing on key signalling pathways

(e.g., TNF-alpha, IL-6, JAK-STAT, PI3K-AKT), immune and stromal cellular interactions within the synovium, and emerging therapeutic platforms including nanocarriers, biomaterials, and cell-based strategies. Findings were synthesized using a thematic framework, aligning disease mechanisms with evolving therapeutic approaches to support a translational perspective. As a narrative review, formal bias assessment and quantitative meta-analysis were not performed; however, priority was accorded to studies demonstrating strong methodological design and scientific consistency.

3. Integrated Immunopathogenesis of Rheumatoid Arthritis

RA evolves through a series of interconnected immunological events progressing from systemic immune activation to localized synovial inflammation and irreversible structural joint damage. Although these phases are described sequentially for conceptual clarity, they are fundamentally interdependent, with continuous interplay among immune cells, synovial stromal elements, and cytokine networks driving disease evolution (Table 1).

Table 1. Risk factors contributing to rheumatoid arthritis development and their associated pathogenic mechanisms driving synovial inflammation and joint destruction.

Risk Factor	Pathogenic Mechanism
Genetic predisposition (HLA-DRB1 alleles)	Synovial infiltration by autoreactive immune cells
Female sex predominance	Crosstalk between fibroblast-like synoviocytes and innate immune populations
Advancing age (middle-aged to elderly)	Elaboration of pro-inflammatory mediators including IL-1, IL-6, IL-17, TNF-alpha, MMPs, and GM-CSF
Obesity and metabolic dysfunction	Activation of T lymphocytes and secretion of Th17-associated cytokines (IL-17, IL-1beta, IL-6)
Microbial infections (bacterial and viral)	Activation and expansion of B cells and synovial macrophages
Environmental exposures (cigarette smoking, pollutants)	Enhanced osteoclast activity and accelerated bone resorption
Non-HLA genetic variants (PTPN22, STAT4, PADI4)	Disproportionate expansion of pro-inflammatory M1 macrophages relative to homeostatic M2 phenotype
Intestinal microbiome dysbiosis	Synovial hyperplasia, joint effusion, pathological angiogenesis, and pannus formation

3.1. Preclinical Phase: Genetic Susceptibility and Immune Sensitization

The earliest stage of RA is shaped by the interplay of inherited susceptibility and environmental triggers. Genetic risk is prominently associated with HLA-DRB1 shared epitope alleles, with additional contributions from non-HLA loci including PTPN22, STAT4, and PADI4, which modulate antigen presentation and immune signalling. Environmental exposures—notably cigarette smoking, mucosal site inflammation, and gut microbiome dysbiosis—facilitate post-translational protein modifications, particularly citrullination, generating immunogenic neoantigens.

These neoantigens drive the production of ACPAs and RF, serological markers detectable years before overt clinical disease manifests. Immune complex formation and complement pathway activation contribute to early systemic immune engagement, establishing the biological substrate for subsequent disease progression [1,3,6–9].

3.2. Early Synovial Phase: Immune Infiltration and Cytokine Activation

With clinical onset, inflammatory activity becomes concentrated within synovial tissue, characterised by infiltration of CD4+ T lymphocytes, B cells, macrophages, dendritic cells, and natural killer cells—marking the transition from systemic autoimmunity to joint-confined pathology. Pro-inflammatory T helper subsets, particularly Th1 and Th17, drive

cytokine elaboration, while B cells sustain autoantibody generation and facilitate antigen presentation. Macrophages serve as primary amplifiers of the inflammatory response through the secretion of TNF- α , IL-1, IL-6, IL-17, and GM-CSF, establishing a self-perpetuating inflammatory milieu that recruits further immune cells and activates synovial components [1,2,10,11].

3.3. Synovial Expansion Phase: Stromal Cell Activation and Cellular Crosstalk

Sustained inflammation induces activation and proliferation of fibroblast-like synoviocytes (FLS), which acquire an invasive and hyperplastic phenotype, contributing to pannus formation and the elaboration of matrix-degrading enzymes and pro-inflammatory mediators. Single-cell and spatial transcriptomic investigations have revealed substantial FLS heterogeneity, with discrete subsets governing inflammation, fibrosis, and extracellular matrix remodelling. The resulting stromal-immune interface—shaped by cytokine gradients and intercellular signalling—sustains a pathological microenvironment that perpetuates disease activity [12].

3.4. Immune Dysregulation Phase: Loss of Regulatory Homeostasis

A cardinal feature of established RA is the collapse of immune regulatory balance, characterized by dominance of pro-inflammatory M1 macrophages over homeostatic M2 phenotypes, and an imbalance between Th17 cells and regulatory T cells (Tregs). These shifts impair resolution of inflammation and sustain chronic immune activation. Dysregulation of tolerogenic mechanisms—including reduced indoleamine 2,3-dioxygenase (IDO) activity—further reflects compromised immune tolerance and reinforces pro-inflammatory cytokine production within the synovial microenvironment [13].

3.5. Destructive Phase: Osteoimmune Activation and Structural Damage

In advanced disease, progressive joint destruction is mediated principally by osteoclast activation through the RANK/RANKL/OPG signalling axis, culminating in bone resorption and articular erosion. Concurrent synovial angiogenesis and continued pannus expansion sustain inflammatory cell infiltration and perpetuate tissue injury—the cumulative result of prolonged immune-stromal crosstalk leading to irreversible cartilage degradation, bone loss, and functional disability [10,14].

3.6. Cellular and Cytokine Dynamics in the RA Synovium

High-resolution techniques including single-cell RNA sequencing, spatial transcriptomics, and multiplex immunohistochemistry have identified distinct synovial fibroblast (SF) subpopulations within the RA synovium, each with unique functional contributions shaped by local cytokine gradients [15]. Principal SF subsets include PRG4⁺ lining cells that maintain tissue homeostasis, CXCL12⁺ sublining fibroblasts that propagate inflammation, POSTN⁺ populations associated with fibrotic remodelling, and MFAP5⁺ cells involved in provisional matrix deposition—the last of which is preferentially expanded in the lymphomyeloid pathotype of RA compared with psoriatic arthritis or spondyloarthritis [15].

Pro-inflammatory cytokine gradients—including TNF- α , IFN- γ , and IL-1 β —selectively expand pathogenic fibroblast subsets, while cellular crosstalk between natural killer cells, macrophages, and synovial fibroblasts further amplifies leukocyte recruitment and osteoclast-activating signals [16,17]. Upregulation of IDO within the inflammatory infiltrate signals deficient immune tolerance. Collectively, these findings reveal a spatially dynamic immunopathogenesis amenable to stratified cytokine-directed therapies and position the synovial microenvironment as a compelling target for immunoengineering interventions [11,17].

4. Precision and Systems Medicine in Rheumatoid Arthritis

Cytokine–protein interaction network analyses in synovial fibroblasts have identified STAT3/IL-6 signalling as a central regulatory hub, yielding actionable insights into targetable vulnerabilities for selective pathway modulation [13]. Disease stratification using validated biomarkers—such as CHI3L1, placental growth factor (PGF), and calprotectin—enables categorization of patients into clinically meaningful subtypes, including the pauci-immune fibrotic and myeloid-diffuse hyperplastic endotypes, thereby guiding individualized prognostication and therapeutic selection [1]. Integrative multi-omics tools further refine treatment decisions by anticipating responses to biologic agents and identifying patient subgroups at risk of inadequate response to IL-6 inhibition or JAK inhibitor therapy [7].

Advanced spatial immunomapping provides real-time tracking of synovial pathotype evolution, enabling treat-to-target optimization while avoiding unnecessary therapeutic escalation [15]. Taken together, these approaches facilitate the development of tailored combinatorial treatments aimed at achieving histopathological remission and sustained preservation of joint integrity [15,18] (Table 2).

Table 2. Systems-level precision medicine approaches for personalized management of rheumatoid arthritis, integrating molecular profiling, endotype stratification, and multi-omics prediction.

Approach	Core Mechanism	Clinical Relevance
Cytokine–protein network mapping	Identification of STAT3/IL-6 signalling hubs in synovial fibroblasts	Guides selective modulation of therapeutic vulnerabilities
Synovial endotype stratification	Biomarker-based classification (CHI3L1, PGF, calprotectin) into pathotype subgroups	Informs personalized prognosis and therapeutic sequencing
Integrative multi-omics analysis	Prediction of biologic response and JAK inhibitor pairing outcomes	Reduces secondary treatment failure
Spatial transcriptomic immunomapping	Real-time visualization of synovial pathotype dynamics	Supports treat-to-target protocols and prevents over-escalation
Combined clinical impact	Individually tailored combinatorial interventions	Promotes histopathological remission and long-term joint preservation

5. Contemporary Immunotherapeutic Approaches for Rheumatoid Arthritis

The clinical management of RA encompasses a range of treatment modalities, including conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic DMARDs (bDMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and emerging cell-based and engineered therapeutic platforms.

5.1. Conventional DMARDs

Conventional synthetic DMARDs constitute the established backbone of RA pharmacotherapy, operating through broad immunosuppressive mechanisms to attenuate the hyperactive immune response responsible for progressive joint inflammation and structural damage. Representative agents include methotrexate (MTX), sulfasalazine, sodium aurothiomalate (gold salts), leflunomide, and hydroxychloroquine. Despite continued evolution of the RA treatment landscape, csDMARDs retain a central role—particularly in patients with moderate disease activity or those who are unable to tolerate more advanced therapeutic options.

5.2. Achievements and Limitations of Current Therapies

Current RA pharmacotherapies have markedly transformed clinical outcomes, enabling remission or low disease activity in a meaningful subset of patients when ad-

ministered early and aggressively [1]. Methotrexate, the cornerstone csDMARD, offers oral convenience and broad immunomodulatory activity; however, it is associated with hepatotoxicity, gastrointestinal intolerance, and inconsistent efficacy across disease phenotypes [18,19].

Biologic DMARDs directed against TNF-alpha (e.g., etanercept, adalimumab), IL-6 (e.g., tocilizumab), or B-cell populations (e.g., rituximab) confer superior radiographic and functional outcomes, particularly in seropositive disease [20,21]. JAK inhibitors (e.g., tofacitinib, baricitinib)—classified as targeted synthetic DMARDs—offer oral administration with rapid onset by broadly suppressing downstream JAK-STAT-mediated cytokine signalling [22,23]. Despite these advances, approximately 30–40% of patients demonstrate inadequate initial responses or secondary treatment failure, compounded by high treatment costs, immunosuppression-related opportunistic infections, and paradoxical disease flares. These limitations—encompassing off-target systemic effects, immunogenicity, and incomplete pathway inhibition—underscore the rationale for precision immunoengineering approaches that integrate nanocarrier systems, exosomal delivery platforms, and biomaterial scaffolds to achieve spatiotemporal therapeutic precision, multi-target modulation, and minimized toxicity [23].

5.3. Mesenchymal Stem Cell and Immune Cell Therapies

Mesenchymal stromal cells (MSCs) represent a compelling immunomodulatory strategy for RA patients who have failed conventional DMARDs and biologic agents. Acting through paracrine mechanisms—including IDO-mediated tryptophan depletion, PGE2/TGF-beta suppression of Th1 and Th17 lineages, and promotion of M2 macrophage and Treg predominance—MSCs restore synovial homeostasis and yield clinically meaningful reductions in disease activity (DAS28-CRP decrease ≥ 1.5) and disability scores (HAQ-DI improvement) [24].

Phase I/II trials and meta-analyses confirm MSCs' favourable safety profile (serious adverse events < 5%; no tumorigenicity demonstrated) and efficacy in early erosive RA, with infusions normalising CRP, ESR, and autoantibody titres through reprogramming of the synovial stromal-vascular niche [25]. MSCs exert their therapeutic effects through prostaglandin E2, TGF-beta, and IL-10 secretion, shifting macrophage polarisation from pro-inflammatory M1 toward anti-inflammatory M2 phenotypes, downregulating APRIL and BAFF on B cells, and expanding Foxp3+ Tregs while suppressing pro-inflammatory Th17 populations [26–29]. Extracellular vesicles (EVs) derived from MSCs further contribute to these therapeutic effects as paracrine mediators, displaying anti-inflammatory activity within the local tissue microenvironment [30].

Clinical evidence supporting MSC efficacy includes a Chinese trial (NCT01547091) demonstrating significant disease remission with reductions in CRP, RF, and anti-CCP antibody levels sustained at both 8 months and 3 years of follow-up [30]. A Spanish randomized multicentre trial (NCT01663116) corroborated the regulatory capacity of adipose-derived MSCs (AD-MSCs) in RA management. However, rigorous optimization of cell source selection, dosing regimens, and administration routes in large randomized trials remains necessary to standardize protocols and confirm long-term therapeutic durability.

Hydrogel encapsulation strategies have emerged as a promising method for enhancing MSC delivery and localizing therapeutic effects. In RA-induced rodent models, chondroitin sulfate-based hydrogels encapsulating MSCs significantly reduced joint inflammation and improved articular function relative to controls. Similarly, alginate/poly-L-lysine/alginate (APA) hydrogel systems encapsulating MSCs demonstrated reduced inflammation and cartilage degradation through inhibition of IL-1 receptor signalling—suggesting that hydrogel-

based delivery can enhance MSC retention and mitigate systemic adverse effects, though further optimization is required [31].

Beyond MSCs, immune cell populations including macrophages, dendritic cells (DCs), and B cells contribute distinctly to RA pathogenesis and represent exploitable therapeutic targets. Macrophages amplify synovial inflammation through pro-inflammatory cytokine and chemokine production; ex vivo engineering or pharmacological manipulation to promote M2 polarisation—or their targeted depletion to interrupt M1-driven synovial infiltration—represents a promising therapeutic approach [32]. DCs regulate adaptive immunity through T-cell activation, and their modulation may alleviate joint inflammation. B cells sustain autoimmunity through citrullinated protein autoantibody production and are targeted by rituximab-based strategies. Tuftsin-modified alginate nanoparticles have been identified as a candidate tool for macrophage activity modulation [32].

6. Immunoengineering Approaches for Rheumatoid Arthritis

Conventional csDMARDs, biomacromolecular biologics, and cellular therapies face intrinsic limitations including restricted delivery efficiency, immunogenic potential, and suboptimal targeting accuracy. Immunoengineering approaches have emerged to overcome these barriers through the application of nanotechnology and biomaterial science to enhance therapeutic precision while minimizing systemic toxicity.

Immunoengineering encompasses the deliberate design and construction of immune-responsive nanotechnology platforms and biomaterial scaffolds, developed through mechanism-guided immunological principles. This bottom-up engineering paradigm aims to selectively modulate critical immunological pathways, recalibrating cellular responses within the RA synovium to improve therapeutic outcomes.

6.1. Immunomodulatory Biomaterials and Macrophage Reprogramming

Immunomodulatory biomaterials promote bone regeneration at RA-related erosion sites by rebalancing the osteoimmune microenvironment. Their principal mechanism involves macrophage reprogramming from the destructive M1 phenotype—characterized by secretion of TNF-alpha, IL-1beta, and IL-6—toward the reparative M2 phenotype, which produces anti-inflammatory IL-10, arginase-1 (Arg-1), and CD206, thereby suppressing osteoclastogenesis while stimulating osteogenesis, vascular ingrowth, and tissue integration.

Macrophages function as the primary immunological interface at the biomaterial-host boundary, with their activation state governing scaffold integration outcomes. M1 macrophages, driven through NF-kappaB and STAT1 signalling, amplify inflammatory cascades analogous to RA flares. Conversely, M2 polarisation—induced through STAT6, PI3K-AKT, and PPARgamma pathways—releases BMP-2, TGF-beta, and VEGF, mobilising regenerative progenitor cells and promoting vasculogenesis. Optimised cytokine delivery sequences—employing early IFN-gamma exposure followed by IL-4-mediated M2 consolidation—achieve 18–20% increases in M2 macrophage representation and two-fold VEGF upregulation in fibrin-based matrices [32,33] (Tables 3 and 4).

Calcium silicate scaffolds doped with Mg^{2+} and Mn^{2+} ions exemplify this approach: sustained ion release exceeding 28 days neutralises reactive oxygen species (ROS) and inducible nitric oxide synthase (iNOS), augments M2 surface markers, and enhances mineralisation capacity (ALP and OPN expression 1.5–2-fold above controls) with concomitant increases in vascular density at cranial defect sites [34,35].

Table 3. Integrative framework aligning sequential stages of RA pathogenesis with corresponding immunoengineering-based intervention strategies.

Disease Stage	Pathobiological Features	Immunoengineering Targets	Mechanistic Basis
Genetic/preclinical	HLA-DRB1, PTPN22 variants; ACPA/RF neoantigen recognition	Modulation of antigen-presenting pathways; early immune tolerance induction	Preventive targeting of upstream immune priming events
Environmental exposure	Smoking, obesity, microbiome disruption; mucosal barrier inflammation	Barrier restoration; correction of microbial dysbiosis	Nanoparticle-assisted delivery at mucosal interfaces
Immune cell infiltration	Th1/Th17 and B cell activation; macrophage-driven cytokine amplification	siRNA-based cellular depletion; M1-to-M2 reprogramming; Treg expansion	MSC and exosome-mediated immune tolerance restoration
Synovial stromal activation	Fibroblast-like synoviocyte (FLS) hyperplasia; matrix metalloproteinase production	JAK/STAT pathway inhibition; MMP suppression; RANKL neutralisation	Scaffold-based local and sustained therapeutic delivery
Advanced destructive phase	Osteoclast-mediated bone erosion; irreversible cartilage destruction	RANKL sequestration; osteoclast suppression; angiogenesis regulation	Biomaterial-based osteoimmune microenvironment remodelling

Table 4. Pathogenic cell types and molecular targets in the RA synovium, with corresponding immunoengineering delivery strategies and anticipated therapeutic outcomes.

Target Cell/Molecule	Pathological Role	Immunoengineering Strategy	Delivery Platform	Expected Outcome
TNF-alpha	Master pro-inflammatory mediator; drives M1 macrophage polarization	Cytokine sequestration; receptor blockade	Liposomes, nanoparticles, gene therapy vectors	Reduced synovial inflammation; M2 macrophage predominance
IL-6	Th17 differentiation; FLS activation and proliferation	Receptor and trans-signalling inhibition	Polymeric nanoparticles, exosomes	Diminished Th17 response; restored Th17/Treg balance
IL-17	Chronic inflammation maintenance; RANKL-mediated osteoclast induction	Upstream pathway suppression; Th17 cell targeting	Exosome-based miRNA delivery	Reduced Th17 frequency; attenuated bone erosion
BAFF	B-cell activation and survival; autoantibody production	siRNA targeting of BAFF receptor expression	Polymeric nanoparticle carriers	Decreased B-cell synovial infiltration; lower autoantibody titres
RANKL	Osteoclast activation; bone resorption and erosion	Direct ligand sequestration; decoy receptor delivery	Biomaterial scaffolds; targeted inhibitor systems	Prevention of bone erosion; osteoblast reactivation
M1 macrophages	TNF-alpha, IL-1beta, IL-6 production; tissue invasion	M1-to-M2 reprogramming via IL-10/TGF-beta delivery	MSC secretomes, exosomes, cytokine-releasing hydrogels	M2 macrophage polarisation; systemic inflammation reduction
Th17 lymphocytes	IL-17 and GM-CSF secretion; tissue-destructive responses	Inhibition of Th17 differentiation; Treg expansion	MSC infusions; exosome-delivered miRNA payloads	Rebalanced Th17/Treg ratio; reduced cartilage damage
Fibroblast-like synoviocytes (FLS)	MMP production; chemokine secretion; pannus tissue formation	JAK/STAT inhibition; targeted apoptosis induction	Ligand-functionalized nanoparticles; micellar delivery systems	Reduced matrix degradation; attenuated immune cell recruitment

6.2. Innovative Scaffold Architectures

Contemporary scaffold architectures replicate bone's hierarchical organisation to optimise immunomodulatory and regenerative outcomes. Key platforms include: (i) PLGA/black phosphorus (BP) three-dimensionally printed scaffolds that utilise BP's photothermal properties and PI3K-AKT-mediated M2 polarisation to achieve M2/M1 ratios exceeding 3:1, resolving steroid-associated osteonecrosis with a two-fold increase in bone volume in rodent femoral defect models [36]; (ii) MnCO₃/DFO@PCL-GelMA/PLLA-HA multilayered structures mimicking osteon architecture, in which H₂O₂-triggered CO and Mn²⁺ release reduces osteoclast activity by 40% (as indicated by TRAP-5b suppression) and triples vascularisation through HIF-1alpha induction [4]; and (iii) nanotopographic PLGA systems incorporating MgO-alendronate conjugates and Sr²⁺-doped silicates that activate Wnt/beta-catenin signalling, yielding 1.8-fold higher apatite deposition and enhanced mineralisation [37].

To circumvent bioinert limitations, scaffolds are increasingly co-functionalized with VEGF/BMP-2 concentration gradients and piezoelectric nanoparticles (e.g., whitlockite), achieving 8.6% endothelial cell coverage and 1.8-fold pericyte enrichment in vivo.

Alendronate-Mg²⁺ hybrid systems, tailored to RA's TNF/IL-17-enriched milieu, normalise CRP and ESR without mechanical loosening risks [38]. While predominantly in the pre-clinical phase, key translational challenges include Th17 persistence and corticosteroid-mediated interference. Exosome-ion hybrid constructs are positioned for RA-focused clinical trials, offering promise for personalised, erosion-targeted regenerative therapies [33] (Table 5).

Table 5. Comparative overview of conventional and immunoengineered therapeutic modalities for RA, encompassing mechanisms of action and associated adverse effect profiles.

Therapeutic Class	Representative Agents	Mechanism of Action	Principal Adverse Effects	Clinical Limitations
Conventional DMARDs	Methotrexate, sulfasalazine, leflunomide	Broad immunosuppression; nucleotide biosynthesis inhibition	Hepatotoxicity, myelosuppression, gastrointestinal intolerance	Limited bioavailability; narrow therapeutic index; 30–40% non-response rate
Biologic DMARDs	Anti-TNF (adalimumab, etanercept), anti-IL-6 (tocilizumab), anti-CD20 (rituximab)	Targeted neutralisation of inflammatory cytokines or B cells via monoclonal antibodies	Elevated infection risk; immunogenicity; injection site reactions	High economic cost; systemic immunosuppression; paradoxical disease flares
JAK inhibitors	Tofacitinib, baricitinib	Downstream STAT signalling suppression across multiple cytokine pathways	Dyslipidaemia; thromboembolic risk; opportunistic infections	Off-target immunomodulation; variable pharmacokinetics
Mesenchymal stem cells	Autologous/allogeneic MSCs; adipose-derived MSCs	Paracrine immunomodulation via IDO, PGE2, TGF-beta; M2 polarization; Treg expansion	Potential immune reactions; uncertain long-term tumorigenicity	Heterogeneous efficacy; manufacturing variability; limited long-term clinical data
Nanoparticle delivery systems	Liposomes, polymeric micelles, PLGA nanoparticles	Targeted synovial delivery; sustained drug release; reduced systemic distribution	Potential nanoparticle-related toxicity; immune activation; bioaccumulation risk	Regulatory uncertainty; scalability challenges in GMP manufacturing
Exosome-based platforms	MSC-derived exosomes; engineered extracellular vesicles	Cell-free immunomodulation through miRNA and protein cargo delivery	Batch-to-batch variability; potential immunogenicity	Standardisation and scalability challenges; limited in vivo stability data
Biomaterial scaffolds	Injectable hydrogels; 3D-printed composites; ion-doped scaffold systems	Localised, sustained drug release; osteoimmune microenvironment remodelling	In vivo degradation variability; immune clearance; integration complications	Predominantly preclinical evidence; surgical implantation required

7. Nanotechnology for RA Management

Nanotechnology constitutes a transformative advancement in immunoengineering, enabling the targeted delivery of therapeutic payloads to specific immune cell populations and tissue compartments [14]. Methotrexate, the most widely utilised folate antagonist in RA management, suppresses immune cell proliferation but is hampered by poor bioavailability and substantial adverse effects including hepatotoxicity and myelosuppression [39,40]. Nanocarrier strategies—encompassing liposomes, polymeric micelles, and solid nanoparticles—exploit the enhanced permeability and retention (EPR) effect to improve synovial drug accumulation, encapsulating therapeutic agents to protect them from premature degradation and modulating pharmacokinetic profiles [41]. Surface functionalisation with targeting ligands such as antibodies, peptides, or small molecules further refines tissue-specific delivery, reduces off-target exposure, and permits dose reduction while preserving therapeutic efficacy.

Nanotechnology-based platforms overcome fundamental limitations of conventional RA therapy—including non-specific biodistribution, rapid systemic clearance, and inadequate synovial tissue penetration—by enabling precise accumulation at inflamed joints through both the EPR effect and receptor-mediated active targeting (e.g., via folate receptors). These systems support sustained drug release kinetics, combinatorial payload delivery (e.g., DMARDs co-administered with siRNA constructs), and reduced dosing frequency, collectively improving both therapeutic efficacy and tolerability [42].

7.1. Liposome-Based Drug Delivery in RA

Liposomes are nanoscale spherical vesicles assembled from phospholipid bilayers, capable of encapsulating molecules across a broad range of aqueous and lipid solubility.

Preclinical studies have consistently demonstrated enhanced drug accumulation at sites of synovial inflammation and measurable reductions in inflammatory cytokine expression. Ren et al. showed that modifying liposome size, surface charge, and PEG chain length substantially improved targeted dexamethasone delivery, increasing joint retention and uptake by synovial fibroblasts and macrophages [43]. Beyond MTX, liposomal catalase delivery has been investigated by Chen et al., employing POPC/FOL-S100/cholesterol vesicles designed to selectively target activated macrophages and catalytically decompose hydrogen peroxide—thereby augmenting MTX's therapeutic effects [44]. Glucocorticoids and tofacitinib have similarly demonstrated improved therapeutic profiles when delivered through liposomal formulations [45].

7.2. Exosomes in RA Therapy

Exosomes—extracellular vesicles secreted by parental cells including MSCs and macrophages—possess inherent anti-inflammatory and tissue-reparative properties. Engineered exosomes derived from umbilical cord MSCs (TAXI-exosomes) have demonstrated immunomodulatory activity in autoimmune neuroinflammation models, repolarising pro-inflammatory M1 microglia toward anti-inflammatory M2 phenotypes through TNF pathway suppression and cytokine profile modulation (upregulating IL-4, IL-10, and TGF-beta while suppressing IL-17A, TNF-alpha, and IFN-gamma)—a paradigm directly applicable to RA synovitis, given the analogous macrophage-cytokine pathophysiology of the inflamed joint.

Exosomes regulate RA disease activity through delivery of microRNAs (miRNAs), proteins, and enzymes that attenuate immune cell infiltration into affected joints [46]. Zhang et al. developed neutrophil-derived exosomes surface-modified with ultrasmall Prussian blue nanoparticles (uPB-Exo) via click chemistry, which modulated FLS activation and the TH17/Treg signalling axis, effectively reducing joint inflammation and structural damage [42]. Similarly, Tang et al. engineered anti-inflammatory exosomes (AI-Exo) incorporating IL-10 to facilitate M2 macrophage polarisation and attenuate RA-associated tissue injury [47].

MSC-derived exosomes carrying miRNAs that activate PI3K-AKT/PPARgamma pathways for M2 macrophage polarisation are of particular relevance; when integrated into biomaterial scaffolds, EV-loaded constructs can further amplify osteoimmunomodulatory effects [33]. Preclinical evidence demonstrates MSC-derived exosomes attenuate RA synovitis without adverse safety signals, positioning them as candidates for refractory disease clinical trials, though synovial pharmacokinetics and interactions with Th17-mediated pathways require further characterisation [48–50].

7.3. Polymeric Nanoparticles for Targeted RA Therapy

Polymeric nanoparticles—fabricable from metals, natural and synthetic polymers, lipids, and proteins in the 1–100 nm size range—offer versatile platforms for RA drug delivery. Lyu et al. developed mannose-surface-modified MTX-loaded nanoparticles (MTX-M-NPs) designed to selectively engage neutrophils, demonstrating meaningful reductions in inflammatory cytokine levels and bone degradation in preclinical models [51,52]. Wu et al. further exploited nanoparticle-mediated delivery of siRNA targeting the BAFF receptor (siBAFF) on B cells, achieving reduced B-cell synovial infiltration and inflammatory activity with potential to lower circulating anti-collagen autoantibody titres [53].

7.4. Advanced Nanocarrier Systems

Hybrid nanoparticle architectures combining liposomal and gold components—exemplified by the LGNP-CoQ10 system described by Jhun et al.—demonstrate efficacy in targeting the STAT3/Th17 signalling axis, a critical inflammatory regulator in RA, with improved delivery precision and cytokine suppression [54]. Emerging constructs such as stable metal-organic frame-

work nanoparticles hold additional promise; Li et al. developed chondroitin sulfate-based prodrug nanoparticles capable of co-delivering chlorin e6 and retinoic acid to diminish photodynamic therapy-induced immunosuppression through Golgi apparatus disruption and selective inhibition of immunosuppressive cytokine synthesis [55].

Viral gene therapy vectors represent another frontier approach. Adriaansen et al. designed an adeno-associated virus (rAAV5.NFkB-TNFRI-Ig) encoding a chimeric disease-inducible TNF-alpha blocker fused to an immunoglobulin Fc region, enabling activity-responsive TNF blockade with minimised systemic effects [56]. Complementary preclinical work employing AAV5-mediated human interferon-beta (hIFN-beta) delivery demonstrated further reductions in inflammation and joint damage, supporting the potential of highly targeted, low-toxicity gene therapeutic strategies for RA (Tables 6 and 7).

Table 6. Overview of nanotechnology-based therapeutic delivery platforms for RA, including material composition, active cargo, mechanistic action, and key preclinical outcomes.

Platform	Composition	Active Payload	Mechanism of Action	Preclinical Outcome	Refs.
Liposomes	Phospholipid bilayer; PEGylated surface coating	Methotrexate, dexamethasone, catalase	EPR-mediated synovial accumulation; folate receptor macrophage targeting; ROS decomposition	Reduced TNF-alpha, IL-6, IL-17; 2–3x increased synovial drug retention	[43–45]
Polymeric nanoparticles	PLGA, chitosan, alginate; mannose-modified surfaces	Methotrexate, siRNA (BAFF), JAK inhibitors	Receptor-targeted cellular uptake; intracellular release; sustained pharmacokinetics	Reduced inflammatory infiltrate; lower anti-collagen antibodies; bone erosion prevention	[51–53]
Hybrid nanoparticles	Liposome-gold composites; PLGA-ion conjugates	CoQ10, iron oxide, small molecules	Photothermal activation; multi-modal imaging; enhanced drug encapsulation	STAT3/Th17 axis suppression; reduced joint structural damage; imaging capability	[33,54]
MSC-derived exosomes	Lipid bilayer vesicles; 30–200 nm diameter	miRNA (miR-223, miR-146a), IDO, TGF-beta, proteins	Receptor-mediated endocytosis; intracellular miRNA delivery; M2 polarization; paracrine modulation	M1-to-M2 reprogramming; elevated Treg frequency; Th17 suppression; improved vascularisation	[46,49,50]
Engineered exosomes	Neutrophil-derived membrane; uPB-modified surface	Ultrasmall Prussian blue (uPB); catalytic cargo	Multi-modal imaging-therapy integration; catalytic ROS scavenging; FLS modulation	Reduced joint swelling; rebalanced Th17/Treg axis; diminished inflammation and damage	[42]
Metal–organic frameworks	Chondroitin sulfate-based prodrug architecture	Chlorin e6, retinoic acid	Lysosomal/endosomal targeted release; Golgi apparatus disruption; PDT immunosuppression reversal	Suppressed immunosuppressive cytokines; enhanced photodynamic therapeutic efficacy	[55]
Viral gene therapy	Adeno-associated virus serotype 5 (AAV5)	TNF receptor-Ig fusion gene; human IFN-beta	Disease-inducible promoter; sustained local transgene expression; targeted TNF blockade	Attenuated joint inflammation and damage; durable TNF inhibition with low systemic exposure	[56]
Microparticles/ microspheres	MPEG-PCL-MPEG; PLGA/ mPEG copolymers	Etanercept, TGF-beta, rapamycin, IL-2	Intra-articular depot with sustained release up to 90 days; local immunomodulatory payload delivery	Reduced TNF-alpha, IFN-gamma, IL-6, IL-17, MMP-3/-13; decreased arthritis severity and erosion	[57,58]
Polymeric micelles	PCL-PEG; MPEG-PCL-MPEG copolymers	Dexamethasone, methotrexate	Self-assembly; sustained intracellular drug release; enhanced aqueous solubility	Attenuated pro-inflammatory cytokines; improved bone regeneration; reduced osteoclastogenesis	[59,60]

Table 7. Comparative physicochemical characterisation of nanotechnology delivery platforms and their suitability for RA therapeutic applications.

Platform	Size	Composition	Targeting Mode	Cellular Uptake	Active Delivery	Passive Targeting	Status
Liposomes	50–500 nm	Phospholipid bilayer	Folate receptor; mannose; PEG coating	Receptor-mediated endocytosis; macrophage phagocytosis	Antibodies; functionalised ligands	EPR effect in inflamed synovium	Preclinical/early clinical
Polymeric micelles	10–100 nm	Self-assembling PCL-PEG copolymers	Passive; surface-modified variants	Fluid-phase endocytosis	Ligand-modified hydrophobic core	EPR effect; hydrophobic core entrapment	Preclinical
Polymeric NPs	50–500 nm	PLGA, chitosan, alginate	Mannose; hyaluronic acid; antibody surface coating	Phagocytosis; receptor-mediated endocytosis	Cationic surface charge; targeting peptides	Charge-mediated accumulation; EPR	Preclinical/IND
Exosomes	30–150 nm	Bilayer membrane; endocytic origin	Tetraspanin receptor ligands; homing peptides	Receptor–ligand interaction; membrane fusion	Engineered surface proteins; miRNA cargo	Tissue tropism of parent cell type	Preclinical/early trials
Hybrid NPs	50–200 nm	Liposome-metal composites; PLGA-ion conjugates	Dual chemical/physical targeting; surface engineering	Multi-pathway uptake	Magnetic/photo-thermal activation	Enhanced EPR via surface design	Preclinical
MOFs	100–500 nm	Organic-inorganic hybrid lattices	Enzyme-responsive; pH-triggered release	Receptor-mediated; bulk endocytosis	Stimuli-responsive payload release	Structural degradation-mediated	Preclinical
Viral vectors	20–100 nm	Virus capsid; enveloped/non-enveloped	Natural cellular tropism; engineered surface ligands	High-efficiency receptor-specific entry	Nucleic acid transgene expression	Tissue-specific viral targeting	Advanced preclinical
Microspheres	1–100 µm	Solid/hollow polymeric structures	Size-dependent tissue penetration; chemokine gradients	Phagocytosis; depot-based uptake	Sustained bulk release; burst-then-slow kinetics	Particle size-directed accumulation	Preclinical

7.5. Microspheres and Polymeric Micelles in RA Drug Delivery

Microspheres and polymeric micelles have been extensively investigated as controlled-release platforms for RA therapeutics, leveraging their capacity to encapsulate bioactive molecules and extend therapeutic duration. Erdemli et al. reported that MPEG-PCL-MPEG microspheres successfully sustained etanercept release for up to 90 days, achieving significant reductions in TNF- α , IFN- γ , IL-6, IL-17, MMP-3, and MMP-13 in synovial tissue [57]. Bassin et al. developed PLGA/mPEG-based microparticles (TRIM-P) co-delivering TGF- β , rapamycin, and IL-2, demonstrating substantial reductions in arthritis severity scores and bone erosion following intra-articular administration in collagen-induced arthritis models [58]. Wang et al. engineered PCL-PEG micellar systems encapsulating low-dose dexamethasone for targeted inflamed joint delivery, achieving effective reduction in pro-inflammatory cytokines [59]. Xu et al. constructed sialic acid and octadecanoic acid-grafted dextran micelles for MTX encapsulation, demonstrating anti-inflammatory efficacy alongside bone regenerative activity and promotion of osteoblast differentiation [60].

8. Hydrogel-Based Drug Delivery Systems

Hydrogels constitute three-dimensional crosslinked hydrophilic polymer networks capable of retaining large volumes of aqueous media while preserving structural integrity. Derived from both biologically derived (collagen, hyaluronic acid) and synthetic (polyethylene glycol) polymers, hydrogels are valued in biomedical applications for their biocompatibility, high water content, and structural resemblance to native extracellular matrices [61]. Their mechanical properties, degradation kinetics, and biological compatibility can be tailored to replicate specific tissue microenvironments, supporting cell viability, proliferation, and

lineage differentiation. In the context of RA, hydrogels serve as vehicles for NSAIDs and DMARDs, enhancing drug retention at affected joints and minimising systemic toxicity [62].

Both cell-free and cell-laden hydrogel configurations have demonstrated capacity to modulate inflammation and promote tissue repair in preclinical RA models. Injectable and stimuli-responsive hydrogels further enable site-specific therapeutic delivery through minimally invasive routes. However, barriers to clinical translation persist, including limited in vivo structural longevity, susceptibility to immune-mediated clearance, and challenges in scalable manufacture. The complex immunological microenvironment of the RA synovial joint—characterized by diverse immune cell populations and overlapping cytokine signals—further complicates the engineering of hydrogels capable of precisely recalibrating local immune responses.

Gao et al. developed an intra-articular delivery system incorporating camptothecin nanocrystals synthesised through bioorthogonal click chemistry, demonstrating localised and sustained drug release within the inflamed joint compartment [18]. Ma et al. engineered a self-assembling supramolecular hydrogel (GDFDFDY) conjugated to MTX, yielding MTX-GDFDFDY constructs that significantly reduced joint oedema and afforded cartilage protection in RA models [63]. Zhao et al. formulated a flexible liposomal hydrogel system (DS-FLs/DEX) integrating dextran sulfate (DS) with encapsulated dexamethasone (DEX), demonstrating sustained drug release, effective penetration into inflamed synovial tissue, and reductions in joint inflammation and bone degradation [64].

9. Regulatory Crosstalk Between Immunoengineering and Disease Pathogenesis

While immunoengineering platforms are designed to suppress disease mechanisms, this view oversimplifies the reality: disease factors simultaneously dictate whether engineered therapies will succeed or fail. The interplay between engineered constructs and RA pathobiology is fundamentally bidirectional. Immunoengineered nanoparticles, MSCs, and scaffolds don't operate in isolation—they must contend with, and are shaped by, the inflammatory landscape they're meant to repair. Understanding how these systems regulate each other is crucial for predicting clinical responses and optimizing treatment strategies.

9.1. *TNF-Alpha as a Double-Edged Regulator*

TNF-alpha exemplifies this bidirectional control. When nanoparticles or other engineered systems successfully suppress TNF, the benefits cascade: lower TNF means reduced IL-6 and IL-1beta production, which in turn tilts the Th17/Treg balance toward tolerance and reduces RANKL-driven bone erosion. This creates a beneficial negative feedback. But the converse is equally true. In highly inflamed joints where TNF levels remain elevated, these same cytokine networks work against immunoengineering platforms. High TNF increases vascular permeability—which sounds helpful for nanoparticle delivery, but it also floods the synovium with proteases, reactive oxygen species, and complement factors that shred nanoparticles before they reach target cells. This explains why combination approaches (conventional TNF blockers + nanoengineered constructs) often outperform monotherapy: conventional agents lower TNF just enough to create a permissive environment for engineered platforms to work [65].

9.2. *Macrophage Polarization: A Self-Reinforcing System with Hidden Resistance*

Engineered platforms that deliver IL-10, IL-4, and TGF-beta can reprogram macrophages from the pro-inflammatory M1 state toward the repair-promoting M2 state. Once this shift occurs, it becomes self-sustaining: M2 macrophages produce more anti-inflammatory cytokines, recruit Tregs, and suppress Th17 cells. In principle, this is elegant. In practice,

established M1-dominated inflammation creates a wall of resistance. Elevated levels of TNF, IFN-gamma, and GM-CSF continuously push incoming monocytes toward the M1 phenotype [66]. Even as engineered systems try to reprogram existing M1 cells, new M1 recruits arrive faster than M2-promoting signals can convert them. This means success in repolarizing macrophages depends on overwhelming the existing pro-inflammatory signal—using enough engineered construct, or combining it with TNF/IFN-gamma inhibitors to tip the balance [67].

9.3. *The Th17/Treg Tug-of-War: Mutually Antagonistic Control*

Exosomes and MSCs that promote Treg expansion work well in early disease, where Th17 cells have not yet hijacked the inflammatory landscape. But in active RA, where Th17 cells dominate, they actively sabotage Treg development. Th17-derived IL-17A and IL-22 compromise intestinal barrier function, allowing bacterial products to fuel more Th17 differentiation. Th17 cells also reprogram the metabolism of surrounding cells toward glycolysis, an environment unfavorable for Treg stability. In this context, pure Treg-expansion strategies won't work alone. They need concurrent suppression of Th17-supporting pathways (IL-17 blocking, IL-23 inhibition) or metabolic interventions (blocking glucose transporters) that level the playing field. The takeaway: in established inflammatory wiring first [65,67].

9.4. *Bone Erosion: Timing Is Everything*

RANKL-targeted immunoengineering makes mechanistic sense: blocking RANKL prevents osteoclast activation and bone loss. But established erosive disease presents a hostile microenvironment. Osteoclasts actively resorbing bone create acidic pockets (pH 4.5–5.0) and ROS-rich environments that destroy pH-sensitive nanoparticles and degrade exosomes [65]. The resorption lacunae themselves become physical barriers—collagenous and mineralized, they resist passive drug diffusion. High local RANKL concentrations can saturate decoy receptor systems, rendering them ineffective. This is why RANKL-targeting works best early, before massive bone loss. Once significant erosion has occurred, you need additional strategies: suppressing Th17-derived RANKL production (via IL-17 or IL-23 inhibition), using pH-stable nanoparticles, or combining RANKL blockade with osteoblast-activating factors (BMP-2, Wnt ligands) to rebuild what's been lost [66].

9.5. *Dysbiosis: A Hidden Amplifier of RA That Regulates Immunoengineering Success*

RA gut dysbiosis—enriched for pro-inflammatory bacteria like *Prevotella* and segmented filamentous bacteria—sustains systemic inflammation through continuous LPS translocation. This creates an underappreciated opportunity: engineered platforms that restore intestinal barrier integrity (exosomes bearing tight-junction proteins, ZO-1-promoting miRNAs) can indirectly suppress the inflammatory burden driving RA. As barrier function improves, beneficial commensals return, butyrate production increases, and Treg expansion follows [2]. However, dysbiotic bacteria actively resist barrier restoration—they thrive in leaky guts. Simply restoring barriers without addressing pathobionts leaves the inflammatory signal intact. Optimal strategies combine both: barrier restoration + pathobiont suppression (via engineered bacteriophages, probiotics delivered in hydrogels, or selective antimicrobial agents). This two-pronged approach addresses both the structural (barrier) and microbial (dysbiosis) components of dysbiosis-driven RA.

9.6. *Anti-CCP: When Antibodies Become Obstacles*

Suppressing TNF and IL-6 reduces PAD4 activation and citrullinated protein generation, creating a self-limiting cycle in anti-CCP production. But in established anti-CCP+ disease, high ACPA titers form immune complexes that activate synovial cells independently of TNF-IL-6 signaling. These complexes deposit in the joint, engage Fc receptors

on macrophages, and activate complement—all mechanisms that persist despite immunoengineering attempts to suppress cytokines. In such cases, immunoengineering strategies need to directly address ACPA production (B cell-depleting constructs, ACPA-neutralizing platforms) rather than relying solely on reducing the initial citrullination driver. Early intervention—before ACPA levels skyrocket—is substantially more effective than treating established anti-CCP-high disease [67] (Table 8).

Table 8. Bidirectional regulatory interactions: How immunoengineering regulates disease factors, and how disease factors regulate immunoengineering efficacy [66].

Disease Factor	How Engineered Therapy Regulates It	How It Constrains Therapy	Clinical Strategy
TNF-alpha elevation	Direct sequestration; suppresses downstream IL-6, IL-1beta, GM-CSF; reduces immune cell recruitment	Creates hostile microenvironment (ROS, proteases, complement); nanoparticles degraded; escape from joint limited by vascular permeability changes	Combine conventional TNF blockade with nanoengineering to reduce inflammatory microenvironment toxicity before engineering takes effect
M1 macrophage dominance	IL-10/IL-4/TGF-beta delivery shifts toward M2; produces anti-inflammatory signals; Treg recruitment	TNF/IFN-gamma continuously push monocytes toward M1; new recruits arrive faster than repolarization; M1-derived ROS degrades anti-inflammatory signals	Use higher engineered payload; add TNF/IFN-gamma inhibitors; consider M1-depleting constructs
Th17 cell expansion	IL-10/TGF-beta expands Tregs; reduces IL-17 production; restores barrier function	IL-17/IL-22 damage barrier; IL-17A reprograms cell metabolism (glycolysis); antagonizes Foxp3; sustains IL-23/IL-17 loop	Concurrent IL-17/IL-23 suppression; metabolic targeting (GLUT1 inhibitors); barrier restoration in parallel
RANKL-driven bone erosion	RANKL sequestration blocks osteoclastogenesis; enables osteoblast activity; BMP/Wnt promote Treg	Acidic resorption pits (pH 4.5) destroy nanoparticles; ROS degrades exosomes; physical barriers prevent diffusion; high RANKL saturates decoys	Early intervention before erosion; pH-stable nanoparticles; suppress Th17-derived RANKL; co-deliver osteogenic factors
Dysbiosis/barrier dysfunction	Barrier restoration (ZO-1 exosomes); pathobiont targeting; restores commensals; Treg expansion via butyrate	Pathobionts thrive in leaky barriers; LPS translocation sustains systemic inflammation independent of local therapy	Combined barrier restoration + dysbiosis correction; engineered bacteriophages; probiotic co-delivery in hydrogels
High anti-CCP/ACPA	TNF/IL-6 suppression reduces PAD4 activation; fewer citrullinated antigens; reduced ACPA production	ACPA-IC complexes independently activate FcgammaR/complement on synovial cells; sustain inflammation despite TNF blockade	Intervene early before ACPA accumulation; add B cell-depleting or ACPA-neutralizing platforms; intense TNF/IL-6 suppression

These bidirectional interactions fundamentally reshape how we should design and deploy immunoengineering strategies. Rather than assuming engineered platforms operate independently, we must acknowledge that their success depends on understanding how disease factors either enable or constrain them. This perspective calls for smarter therapeutic sequencing: using conventional agents to lower inflammatory barriers first, then introducing engineered constructs to exploit the newly permissive environment. It also argues for combination approaches that address multiple regulatory bottlenecks simultaneously—combining Th17 suppression with Treg expansion, barrier restoration with dysbiosis correction—rather than targeting single pathways. Finally, it underscores the importance of early intervention: before disease factors become entrenched and resistant, engineered platforms can work more effectively and require lower doses.

10. Translational Framework: From Pathobiology to Targeted Therapy

Translating mechanistic insights into actionable clinical strategies is central to advancing RA management. An integrated precision framework—encompassing detailed patient profiling, disease stratification, and targeted therapeutic sequencing—enables more adaptive and individualised clinical decision-making.

Comprehensive patient evaluation should extend beyond conventional measures to incorporate: serological markers including ACPAs and RF; inflammatory indices such as CRP and ESR; and emerging biomarkers including calprotectin and CHI3L1. Where technically accessible, synovial tissue characterisation and advanced imaging modalities can further

delineate disease endotypes (lymphoid, myeloid, or fibrotic), supporting individualized therapeutic planning.

Conventional DMARDs—particularly methotrexate—remain the cornerstone of initial pharmacotherapy. Patients presenting with high disease burden or poor prognostic features may benefit from early therapeutic intensification through combination DMARD regimens or expedited introduction of biologic agents. In cases of inadequate response, therapeutic escalation should align with the dominant inflammatory pathway: TNF-driven disease warrants anti-TNF biologics; IL-6-mediated inflammation is addressed with IL-6 inhibitors such as tocilizumab; and broad multi-cytokine activation may benefit from JAK inhibitor therapy.

For refractory or structurally progressive disease, immunoengineering platforms offer targeted immune modulation: nanocarrier systems enable site-specific drug delivery with reduced systemic exposure; MSC therapies promote immune regulation through Treg expansion and macrophage polarisation; exosome-based platforms provide cell-free immunomodulation with improved tissue-targeting; and hydrogel or scaffold-based biomaterial systems permit sustained local drug release while supporting tissue repair and osteoimmunomodulation.

Therapeutic response should be monitored longitudinally using standardised clinical indices (e.g., DAS28), serial biomarker assessment, imaging modalities, and—where feasible—synovial profiling. This treat-to-target approach facilitates timely modifications to therapeutic strategy, promoting sustained remission and preventing structural deterioration. Future RA management will depend on the integration of molecular diagnostics, real-time disease monitoring, and advanced therapeutic platforms, enabling a transition from reactive treatment paradigms to predictive, personalized care.

11. Critical Appraisal and Constraints

Despite substantial conceptual advances, the clinical translation of immunoengineering approaches in RA faces multiple significant barriers. The evidence base remains predominantly preclinical, with limited human data to confirm immunomodulatory efficacy and durability *in vivo*. RA's biological heterogeneity—encompassing diverse immune and stromal endotypes—generates variable therapeutic responses, particularly when broad treatment strategies are applied without patient stratification.

Technical challenges further constrain progress: nanocarrier systems must resolve issues of pharmacokinetics, potential cytotoxicity, and manufacturing scalability; MSC-based therapies face inconsistency in procurement, quantification, and administration protocols; and exosomal platforms are hampered by batch-to-batch variability and production scalability constraints. Single-target cytokine inhibition strategies are additionally vulnerable to adaptive pathway circumvention through signalling redundancy, leaving residual smouldering inflammation. Concurrent influences of corticosteroids, metabolic comorbidities, and gut microbiome alterations on therapeutic outcomes are largely unaddressed by current engineered constructs. Prohibitive development costs and complex regulatory requirements further limit equitable access to emerging therapies. These challenges collectively underscore the need for stratified clinical trials, combinatorial multi-target approaches, and interdisciplinary collaboration to fully realise immunoengineering's therapeutic potential in RA.

12. Summary and Future Directions

Rheumatoid arthritis represents a multifactorial autoimmune disorder orchestrated by interconnected cellular and molecular cascades. Although contemporary pharmacotherapies have significantly advanced disease control, persisting barriers—including incomplete remission rates, off-target toxicity profiles, and biologically refractory phenotypes—reveal substantial unmet clinical need. Immunoengineering is emerging as a precision-based

paradigm capable of orchestrating coordinated modulation of immunological axes through nanotechnological delivery vectors, cellular therapeutics, and biomaterial scaffolds, with compelling preclinical and early clinical support.

Critical priorities include resolving challenges in biocompatibility, scalable production, and sustained therapeutic efficacy to enable clinical adoption. Future investigations combining high-resolution molecular profiling with purpose-designed engineered constructs hold promise for truly individualised, superior therapeutic architectures. Biomaterial-based immunoengineering modalities—including hydrogels, microparticulate depot systems, and nanoparticulate drug carriers—offer transformative potential for synovial immune recalibration, though optimal intra-articular retention and tissue-specificity require further refinement of physicochemical parameters (particle size, zeta potential, surface functionalisation).

Translational insights from oncological immunotherapy—particularly chimeric antigen receptor engineering and synthetic immunobiology—offer applicable conceptual frameworks for RA. Combining disease-modifying agents with bioengineered therapeutic effectors and structured biomaterial matrices may extend remission trajectories and improve synovial immunopathological characterisation. Comprehensive multi-omics interrogation of cytokine networks, intracellular signal transduction pathways, and biomaterial–cellular interface interactions will calibrate next-generation therapeutic interventions, reduce dosing requirements, and expand the potential of musculoskeletal immunotherapy.

Author Contributions: D.M. conceived the review, performed the literature search, analyzed and synthesized the data, and drafted the manuscript. D.M. also prepared the graphical abstract. J.M. critically reviewed the manuscript for scientific accuracy, intellectual content, and clinical relevance, and provided substantive revisions. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Alivernini, S.; Firestein, G.S.; McInnes, I.B. The pathogenesis of rheumatoid arthritis. *Immunity* **2022**, *55*, 2255–2270. [[CrossRef](#)] [[PubMed](#)]
2. Cao, F.; He, Y.-S.; Wang, Y.; Zha, C.-K.; Lu, J.-M.; Tao, L.-M.; Jiang, Z.-X.; Pan, H.-F. Global burden and cross-country inequalities in autoimmune diseases from 1990 to 2019. *Autoimmun. Rev.* **2023**, *22*, 103326. [[CrossRef](#)] [[PubMed](#)]
3. Gao, Y.; Zhang, Y.; Liu, X. Rheumatoid arthritis: Pathogenesis and therapeutic advances. *MedComm* **2024**, *5*, e509. [[CrossRef](#)]
4. Zhang, J.; Tong, D.; Song, H.; Ruan, R.; Sun, Y.; Lin, Y.; Wang, J.; Hou, L.; Dai, J.; Ding, J.; et al. Osteoimmunity-Regulating Biomimetically Hierarchical Scaffold for Augmented Bone Regeneration. *Adv. Mater.* **2022**, *34*, e2202044. [[CrossRef](#)] [[PubMed](#)]
5. Klimak, M.; Nims, R.J.; Pferdehirt, L.; Collins, K.H.; Harasymowicz, N.S.; Oswald, S.J.; Setton, L.A.; Guilak, F. Immunoengineering the next generation of arthritis therapies. *Acta Biomater.* **2021**, *133*, 74–86. [[CrossRef](#)] [[PubMed](#)]
6. Noto, G.; Salvetti, F.; Demaj, A.; Altieri, P.; Chericoni, E.; Ferrigno, E.; Alunno, A.; Puxeddu, I. Pathogenesis of rheumatoid arthritis: One year in review 2025. *Clin. Exp. Rheumatol.* **2025**, *43*, 1533–1540. [[CrossRef](#)] [[PubMed](#)]
7. Mitrović, J.; Hrkač, S.; Tečer, J.; Golob, M.; Posavec, A.L.; Mitrović, H.K.; Grgurević, L. Pathogenesis of Extraarticular Manifestations in Rheumatoid Arthritis. *Biomedicines* **2023**, *11*, 1262. [[CrossRef](#)]
8. Deane, K.D.; Demoruelle, M.K.; Kelmenson, L.B.; Kuhn, K.A.; Norris, J.M.; Holers, V.M. Genetic and environmental risk factors for rheumatoid arthritis. *Best Pract. Res. Clin. Rheumatol.* **2017**, *31*, 3–18. [[CrossRef](#)]
9. Testa, D.; Calvacchi, S.; Petrelli, F.; Giannini, D.; Bilia, S.; Alunno, A.; Puxeddu, I. One year in review 2021: Pathogenesis of rheumatoid arthritis. *Clin. Exp. Rheumatol.* **2021**, *39*, 445–452. [[CrossRef](#)]
10. Gravallese, E.M.; Firestein, G.S. Rheumatoid Arthritis—Common Origins, Divergent Mechanisms. *N. Engl. J. Med.* **2023**, *388*, 529–542. [[CrossRef](#)]

11. Cyndari, K.I.; Scorza, B.M.; Zacharias, Z.R.; Pessôa-Pereira, D.; Strand, L.; Mahachi, K.; Oviedo, J.M.; Gibbs, L.; Butler, K.L.; Ausdal, G.; et al. Resident synovial macrophages in synovial fluid: Implications for immunoregulation. *Clin. Immunol.* **2025**, *271*, 110422. [\[CrossRef\]](#)
12. Hoffmann, M.H.; Kirchner, H.; Krönke, G.; Riemekasten, G.; Bonelli, M. Inflammatory tissue priming: Novel insights and therapeutic opportunities for inflammatory rheumatic diseases. *Ann. Rheum. Dis.* **2024**, *83*, 1233–1253. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Culemann, S.; Grüneboom, A.; Nicolás-Ávila, J.A.; Weidner, D.; Lämmle, K.F.; Rothe, T.; Quintana, J.A.; Kirchner, P.; Krljanac, B.; Eberhardt, M.; et al. Locally renewing resident synovial macrophages provide a protective barrier for the joint. *Nature* **2019**, *572*, 670–675. [\[CrossRef\]](#)
14. Wang, S.; Shi, X.; Li, J.; Huang, Q.; Ji, Q.; Yao, Y.; Wang, T.; Liu, L.; Ye, M.; Deng, Y.; et al. A Small Molecule Selected from a DNA-Encoded Library of Natural Products That Binds to TNF- α and Attenuates Inflammation In Vivo. *Adv. Sci.* **2022**, *9*, e2201258. [\[CrossRef\]](#) [\[PubMed\]](#)
15. Rauber, S.; Mohammadian, H.; Schmidkonz, C.; Atzinger, A.; Soare, A.; Treutlein, C.; Kemble, S.; Mahony, C.B.; Geisthoff, M.; Angeli, M.R.; et al. CD200⁺ fibroblasts form a pro-resolving mesenchymal network in arthritis. *Nat. Immunol.* **2024**, *25*, 682–692. [\[CrossRef\]](#) [\[PubMed\]](#)
16. Wu, L.; Wang, R.; Zhou, Y.; Zhao, D.; Chen, F.; Wu, X.; Chen, X.; Chen, S.; Li, J.; Zhu, J. Natural Killer Cells Infiltration in the Joints Exacerbates Collagen-Induced Arthritis. *Front. Immunol.* **2022**, *13*, 860761. [\[CrossRef\]](#)
17. Cutolo, M.; Campitiello, R.; Gotelli, E.; Soldano, S. The Role of M1/M2 Macrophage Polarization in Rheumatoid Arthritis Synovitis. *Front. Immunol.* **2022**, *13*, 867260. [\[CrossRef\]](#)
18. Gao, Y.; Vogus, D.; Zhao, Z.; He, W.; Krishnan, V.; Kim, J.; Shi, Y.; Sarode, A.; Ukidve, A.; Mitragotri, S. Injectable hyaluronic acid hydrogels encapsulating drug nanocrystals for long-term treatment of inflammatory arthritis. *Bioeng. Transl. Med.* **2021**, *7*, e10245. [\[CrossRef\]](#)
19. Mariani, F.M.; Martelli, I.; Pistone, F.; Chericoni, E.; Puxeddu, I.; Alunno, A. Pathogenesis of rheumatoid arthritis: One year in review 2023. *Clin. Exp. Rheumatol.* **2023**, *41*, 1725–1734. [\[CrossRef\]](#)
20. Zhang, Z.; Liu, Y.; Liang, X.; Wang, Q.; Xu, M.; Yang, X.; Tang, J.; He, X.; He, Y.; Zhang, D.; et al. Advances in nanodelivery systems based on apoptosis strategies for enhanced rheumatoid arthritis therapy. *Acta Biomater.* **2025**, *197*, 87–103. [\[CrossRef\]](#)
21. Knab, K.; Chambers, D.; Kronke, G. Synovial Macrophage and Fibroblast Heterogeneity in Joint Homeostasis and Inflammation. *Front. Med.* **2022**, *9*, 862161. [\[CrossRef\]](#)
22. Bruno, M.C.; Cristiano, M.C.; Celia, C.; D’aVanzo, N.; Mancuso, A.; Paolino, D.; Wolfram, J.; Fresta, M. Injectable Drug Delivery Systems for Osteoarthritis and Rheumatoid Arthritis. *ACS Nano* **2022**, *16*, 19665–19690. [\[CrossRef\]](#)
23. Petrelli, F.; Mariani, F.M.; Alunno, A.; Puxeddu, I. Pathogenesis of rheumatoid arthritis: One year in review 2022. *Clin. Exp. Rheumatol.* **2022**, *40*, 475–482. [\[CrossRef\]](#)
24. Mesa, L.E.; López, J.G.; Quiceno, L.L.; Arroyave, F.B.; Halpert, K.; Camacho, J.C. Safety and efficacy of mesenchymal stem cells therapy in the treatment of rheumatoid arthritis disease: A systematic review and meta-analysis of clinical trials. *PLoS ONE* **2023**, *18*, e0284828. [\[CrossRef\]](#)
25. Song, N.; Scholtemeijer, M.; Shah, K. Mesenchymal Stem Cell Immunomodulation: Mechanisms and Therapeutic Potential. *Trends Pharmacol. Sci.* **2020**, *41*, 653–664. [\[CrossRef\]](#)
26. Li, J.; Qu, Y.; Chu, B.; Wu, T.; Pan, M.; Mo, D.; Li, L.; Ming, Y.; Yang, Y.; Wang, M.; et al. Research Progress on Biomaterials with Immunomodulatory Effects in Bone Regeneration. *Adv. Sci.* **2025**, *12*, e01209. [\[CrossRef\]](#)
27. Kearsley-Fleet, L.; Davies, R.; De Cock, D.; Watson, K.D.; Lunt, M.; Buch, M.H.; Isaacs, J.D.; Hyrich, K.L. Biologic refractory disease in rheumatoid arthritis. *Ann. Rheum. Dis.* **2018**, *77*, 1405–1412. [\[CrossRef\]](#) [\[PubMed\]](#)
28. Ungerer, C.; Quade-Lyssy, P.; Radeke, H.H.; Henschler, R.; Königs, C.; Köhl, U.; Seifried, E.; Schüttrumpf, J. Galectin-9 Is a Suppressor of T and B Cells. *Stem Cells Dev.* **2014**, *23*, 755–766. [\[CrossRef\]](#) [\[PubMed\]](#)
29. Vasilev, G.; Ivanova, M.; Ivanova-Todorova, E.; Tumangelova-Yuzeir, K.; Krasimirova, E.; Stoilov, R.; Kyurkchiev, D. Secretory factors produced by adipose mesenchymal stem cells downregulate Th17 and increase Treg cells in peripheral blood mononuclear cells from rheumatoid arthritis patients. *Rheumatol. Int.* **2019**, *39*, 819–826. [\[CrossRef\]](#) [\[PubMed\]](#)
30. Wang, L.; Wang, L.; Cong, X.; Liu, G.; Zhou, J.; Bai, B.; Li, Y.; Bai, W.; Li, M.; Ji, H.; et al. Human umbilical cord mesenchymal stem cell therapy for patients with active rheumatoid arthritis: Safety and efficacy. *Stem Cells Dev.* **2013**, *22*, 3192–3202. [\[CrossRef\]](#)
31. Wu, F.; Gao, J.; Kang, J.; Wang, X.; Niu, Q.; Liu, J.; Zhang, L. B Cells in Rheumatoid Arthritis: Pathogenic Mechanisms and Treatment Prospects. *Front. Immunol.* **2021**, *12*, 750753. [\[CrossRef\]](#)
32. Jain, S.; Tran, T.H.; Amiji, M. Macrophage repolarization with targeted alginate nanoparticles for arthritis. *Biomaterials* **2015**, *61*, 162–177. [\[CrossRef\]](#) [\[PubMed\]](#)
33. Bi, Z.; Cai, Y.; Shi, X.; Chen, J.; Li, D.; Zhang, P.; Liu, J. Macrophage-mediated immunomodulation in biomaterial-assisted bone repair. *Chem. Eng. J.* **2024**, *488*, 150631. [\[CrossRef\]](#)
34. Du, Z.; Leng, H.; Guo, L.; Huang, Y.; Zheng, T.; Zhao, Z.; Liu, X.; Zhang, X.; Cai, Q.; Yang, X. Calcium silicate scaffolds promoting bone regeneration via the doping of Mg²⁺ or Mn²⁺ ion. *Compos. Part B Eng.* **2020**, *190*, 107937. [\[CrossRef\]](#)

35. Yang, F.; Lv, J.; Huang, Y.; Ma, W.; Yang, Z. A supramolecular assembly strategy for the treatment of rheumatoid arthritis with ultrasound-augmented inflammatory microenvironment reprogramming. *Biomaterials* **2025**, *316*, 123006. [\[CrossRef\]](#)
36. Long, J.; Yao, Z.; Zhang, W.; Liu, B.; Chen, K.; Li, L.; Teng, B.; Du, X.F.; Li, C.; Yu, X.F.; et al. Regulation of Osteoimmune Microenvironment and Osteogenesis by 3D-Printed PLAG/black Phosphorus Scaffolds for Bone Regeneration. *Adv. Sci.* **2023**, *10*, 2302539. [\[CrossRef\]](#) [\[PubMed\]](#)
37. Wang, Y.; Zhang, H.; Hu, Y.; Jing, Y.; Geng, Z.; Su, J. Bone Repair Biomaterials: A Perspective from Immunomodulation. *Adv. Funct. Mater.* **2022**, *32*, 2208639. [\[CrossRef\]](#)
38. Guo, S.; He, C. Bioprinted Scaffold Remodels the Neuromodulatory Microenvironment for Enhancing Bone Regeneration. *Adv. Funct. Mater.* **2023**, *33*, 2304172. [\[CrossRef\]](#)
39. Wang, W.; Zhou, H.; Liu, L. Side effects of methotrexate therapy for rheumatoid arthritis: A systematic review. *Eur. J. Med. Chem.* **2018**, *158*, 502–516. [\[CrossRef\]](#)
40. Swierkot, J.; Szechinski, J. Methotrexate in rheumatoid arthritis. *Pharmacol. Rep.* **2006**, *58*, 473–492.
41. Toy, R.; Roy, K. Engineering nanoparticles to overcome barriers to immunotherapy. *Bioeng. Transl. Med.* **2016**, *1*, 47–62. [\[CrossRef\]](#)
42. Zhang, L.; Qin, Z.; Sun, H.; Chen, X.; Dong, J.; Shen, S.; Zheng, L.; Gu, N.; Jiang, Q. Nanoenzyme engineered neutrophil-derived exosomes attenuate joint injury in advanced rheumatoid arthritis via regulating inflammatory environment. *Bioact. Mater.* **2022**, *18*, 1–14. Erratum in *Bioact. Mater.* **2022**, *19*, 486. [\[CrossRef\]](#)
43. Ren, H.; He, Y.; Liang, J.; Cheng, Z.; Zhang, M.; Zhu, Y.; Hong, C.; Qin, J.; Xu, X.; Wang, J. Role of Liposome Size, Surface Charge, and PEGylation on Rheumatoid Arthritis Targeting Therapy. *ACS Appl. Mater. Interfaces* **2019**, *11*, 20304–20315. [\[CrossRef\]](#) [\[PubMed\]](#)
44. Chen, M.; Daddy J.C., K.A.; Su, Z.; Guissi, N.E.I.; Xiao, Y.; Zong, L.; Ping, Q. Folate Receptor-Targeting and Reactive Oxygen Species-Responsive Liposomal Formulation of Methotrexate for Treatment of Rheumatoid Arthritis. *Pharmaceutics* **2019**, *11*, 582. [\[CrossRef\]](#)
45. Ulmansky, R.; Turjeman, K.; Baru, M.; Katzavian, G.; Harel, M.; Sigal, A.; Naparstek, Y.; Barenholz, Y. Glucocorticoids in nano-liposomes administered intravenously and subcutaneously to adjuvant arthritis rats are superior to the free drugs in suppressing arthritis and inflammatory cytokines. *J. Control. Release* **2012**, *160*, 299–305. [\[CrossRef\]](#)
46. You, D.G.; Lim, G.T.; Kwon, S.; Um, W.; Oh, B.H.; Song, S.H.; Lee, J.; Jo, D.-G.; Cho, Y.W.; Park, J.H. Metabolically engineered stem cell-derived exosomes to regulate macrophage heterogeneity in rheumatoid arthritis. *Sci. Adv.* **2021**, *7*, eabe0083. [\[CrossRef\]](#) [\[PubMed\]](#)
47. Tang, Y.; Wu, Z.; Guo, R.; Huang, J.; Rong, X.; Zhu, B.; Wang, L.; Ma, L.; Cheng, C.; Qiu, L. Ultrasound-augmented anti-inflammatory exosomes for targeted therapy in rheumatoid arthritis. *J. Mater. Chem. B* **2022**, *10*, 7862–7874. [\[CrossRef\]](#)
48. Smith, M.H.; Gao, V.R.; Periyakoil, P.K.; Kochen, A.; DiCarlo, E.F.; Goodman, S.M.; Norman, T.M.; Donlin, L.T.; Leslie, C.S.; Rudensky, A.Y. Drivers of heterogeneity in synovial fibroblasts in rheumatoid arthritis. *Nat. Immunol.* **2023**, *24*, 1200–1210. [\[CrossRef\]](#) [\[PubMed\]](#)
49. Yan, H.C.; Yu, T.T.; Li, J.; Qiao, Y.Q.; Wang, L.C.; Zhang, T.; Li, Q.; Zhou, Y.H.; Liu, D.W. The Delivery of Extracellular Vesicles Loaded in Biomaterial Scaffolds for Bone Regeneration. *Front. Bioeng. Biotechnol.* **2020**, *8*, 1015. [\[CrossRef\]](#)
50. Rasouli, M.; Reynolds, S.T.; Wenke, J.C. Harnessing MSC Immunomodulation in Orthopedics: Clinical Insights for Comorbidities. *Stem Cell Rev. Rep.* **2026**, *22*, 847–874. [\[CrossRef\]](#)
51. Wang, Q.; Qin, X.; Fang, J.; Sun, X. Nanomedicines for the treatment of rheumatoid arthritis. *Acta Pharm. Sin. B* **2021**, *11*, 1158–1174. [\[CrossRef\]](#)
52. Lyu, J.; Wang, L.; Bai, X.; Du, X.; Wei, J.; Wang, J.; Lin, Y.; Chen, Z.; Liu, Z.; Wu, J.; et al. Treatment of RA by Serum Albumin Nanoparticles Coated with Mannose to Target Neutrophils. *ACS Appl. Mater. Interfaces* **2021**, *13*, 266–276. [\[CrossRef\]](#)
53. Wu, H.; Su, S.; Wu, Y.; Wu, Y.; Zhang, Z.; Chen, Q. Nanoparticle-facilitated delivery of BAFF-R siRNA for B cell intervention and RA therapy. *Int. Immunopharmacol.* **2020**, *88*, 106933. [\[CrossRef\]](#)
54. Jhun, J.; Moon, J.; Ryu, J.; Shin, Y.; Lee, S.; Cho, K.-H.; Kang, T.; Cho, M.-L.; Park, S.-H. Liposome/gold hybrid nanoparticle encoded with CoQ10 (LGNP-CoQ10) suppressed rheumatoid arthritis via STAT3/Th17 targeting. *PLoS ONE* **2020**, *15*, e0241080. [\[CrossRef\]](#)
55. Li, H.; Deng, C.; Tan, Y.; Dong, J.; Zhao, Y.; Wang, X.; Yang, X.; Luo, J.; Gao, H.; Huang, Y.; et al. Chondroitin sulfate-based prodrug nanoparticles enhance photodynamic immunotherapy via Golgi targeting. *Acta Biomater.* **2022**, *146*, 357–369. [\[CrossRef\]](#)
56. Adriaansen, J.; Khoury, M.; de Cortie, C.J.; Fallaux, F.J.; Bigey, P.; Scherman, D.; Gould, D.J.; Chernajovsky, Y.; Apparailly, F.; Jorgensen, C.; et al. Reduction of arthritis following intra-articular administration of an adeno-associated virus serotype 5 expressing a disease-inducible TNF-blocking agent. *Ann. Rheum. Dis.* **2007**, *66*, 1143–1150. [\[CrossRef\]](#) [\[PubMed\]](#)
57. Erdemli, O.; Ozen, S.; Keskin, D.; Usanmaz, A.; Batu, E.D.; Atila, B.; Tezcaner, A. In vitro evaluation of effects of sustained anti-TNF release from MPEG-PCL-MPEG and PCL microspheres on human rheumatoid arthritis synoviocytes. *J. Biomater. Appl.* **2014**, *29*, 524–542. [\[CrossRef\]](#) [\[PubMed\]](#)

58. Bassin, E.J.; Buckley, A.R.; Piganelli, J.D.; Little, S.R. TRI microparticles prevent inflammatory arthritis in a collagen-induced arthritis model. *PLoS ONE* **2020**, *15*, e0239396. [[CrossRef](#)] [[PubMed](#)]
59. Wang, Q.; Jiang, J.; Chen, W.; Jiang, H.; Zhang, Z.; Sun, X. Targeted delivery of low-dose dexamethasone using PCL-PEG micelles for effective treatment of rheumatoid arthritis. *J. Control. Release* **2016**, *230*, 64–72. [[CrossRef](#)]
60. Xu, X.-L.; Li, W.-S.; Wang, X.-J.; Du, Y.-L.; Kang, X.-Q.; Hu, J.-B.; Li, S.-J.; Ying, X.-Y.; You, J.; Du, Y.-Z. Endogenous sialic acid-engineered micelles: A multifunctional platform for on-demand methotrexate delivery and bone repair of rheumatoid arthritis. *Nanoscale* **2018**, *10*, 2923–2935. [[CrossRef](#)]
61. Lev, R.; Seliktar, D. Hydrogel biomaterials and their therapeutic potential for muscle injuries and muscular dystrophies. *J. R. Soc. Interface* **2018**, *15*, 20170380. [[CrossRef](#)]
62. BaoLin, G.; Ma, P.X. Synthetic biodegradable functional polymers for tissue engineering: A brief review. *Sci. China Chem.* **2014**, *57*, 490–500. [[CrossRef](#)]
63. Ma, S.; Gu, S.; Zhang, J.; Qi, W.; Lin, Z.; Zhai, W.; Zhan, J.; Li, Q.; Cai, Y.; Lu, Y. Robust drug bioavailability and safety for RA therapy using D-amino acids-based supramolecular hydrogels. *Mater. Today Bio* **2022**, *15*, 100296. [[CrossRef](#)]
64. Zhao, Y.-P.; Han, J.-F.; Zhang, F.-Y.; Liao, T.-T.; Na, R.; Yuan, X.-F.; He, G.-B.; Ye, W. Flexible nano-liposomes-based transdermal hydrogel for targeted delivery of dexamethasone for RA therapy. *Drug Deliv.* **2022**, *29*, 2269–2282. [[CrossRef](#)] [[PubMed](#)]
65. Xia, X.; He, C.; Xue, Z.; Wang, Y.; Qin, Y.; Ren, Z.; Huang, Y.; Luo, H.; Chen, H.N.; Zhang, W.H.; et al. Single cell immunoprofile of synovial fluid in rheumatoid arthritis with TNF/JAK inhibitor treatment. *Nat. Commun.* **2025**, *16*, 2152. [[CrossRef](#)] [[PubMed](#)]
66. Sakthiswary, R.; Uma Veshaliini, R.; Chin, K.Y.; Das, S.; Sirasanagandla, S.R. Pathomechanisms of bone loss in rheumatoid arthritis. *Front. Med.* **2022**, *9*, 962969. [[CrossRef](#)]
67. Peng, Y.; Zhou, M.; Yang, H.; Qu, R.; Qiu, Y.; Hao, J.; Bi, H.; Guo, D. Regulatory Mechanism of M1/M2 Macrophage Polarization in the Development of Autoimmune Diseases. *Mediat. Inflamm.* **2023**, *2023*, 8821610. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.