

Nanocarrier based drug delivery for rheumatoid arthritis: Current strategies and future directions

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ABSTRACT

The application of nanotechnology in drug delivery systems has attracted considerable scientific interest, particularly with respect to improving the therapeutic efficacy and safety profiles of pharmacological agents. This review critically examines nanotechnology-based drug delivery systems for the management of rheumatoid arthritis (RA), a chronic systemic autoimmune disease characterized by persistent synovial inflammation, progressive joint destruction, and significant extraarticular sequelae. Conventional pharmacological strategies such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), and biological disease-modifying antirheumatic drugs (bDMARDs) provide disease control but are associated with significant adverse effects upon prolonged use, inadequate joint specific drug concentrations, and limited responsiveness in a subset of patients. Nanotechnology offers a compelling therapeutic solution by enabling targeted drug delivery to inflamed synovial tissue, thereby enhancing bioavailability, reducing systemic toxicity, and extending drug half-life. This review discusses diverse nanotechnology platforms, such as liposomes, dendrimers, polymeric nanoparticles, hydrogels, metal, inorganic nanoparticles, nucleic acid-based carriers, and stimuli-responsive nanocarriers evaluated for RA treatment. The evidence underscores the potential of these systems to overcome the limitations of traditional therapies and to facilitate precision therapeutics in RA. The review also addresses existing challenges in nanomedicine translation, such as inter-patient variability, protein corona formation, endosomes (as a barrier), biocompatibility, and the need for rigorous clinical validation, while outlining future directions including exosome mediated delivery, biomimetic nanocarriers, and stimuli-responsive platforms.

Keywords: nanotechnology, rheumatoid arthritis, nanocarrier, drug delivery, synovial targeting

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INTRODUCTION

Nanotechnology encompasses the science and engineering of structures and devices with at least one dimension at the nanoscale conventionally defined as 1 to 100 nm. The conceptual foundations of the field were articulated by physicist Richard Feynman in his

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landmark 1959 lecture and the discipline has since evolved into a transformative platform with applications spanning medicine, electronics, energy, environmental science, and beyond (1). At the nanoscale, materials may exhibit physicochemical properties that differ substantially from their bulk counterparts, including altered optical, electrical, magnetic, catalytic, and mechanical characteristics (2). These properties arise from quantum effects, increased surface energy, and the high proportion of atoms located at or near the particle surface, providing opportunities to engineer nanomaterials for specific biological and therapeutic functions (3).

In the biomedical context, nanotechnology is employed across diagnostics, biosensing, drug delivery, tissue engineering, and targeted therapeutics. The rationale for using nanoparticles in medicine is rooted in scale compatibility: many biologically relevant macromolecules operate in the 1–100 nm range, making nanoscale constructs naturally suited for interaction with cellular machinery (4). The distinctive physical, chemical, and biological properties of nanomaterials, including high surface-to-volume ratio, tunable surface chemistry, size-dependent pharmacokinetics, and capacity for surface functionalization confer advantages such as enhanced bioavailability, improved cellular uptake, and site-specific drug release (5). Importantly, the size, shape, surface charge, hydrophobicity, composition, and colloidal stability of nanoparticles can significantly affect protein adsorption, cellular internalization, biodistribution, circulation time, and elimination (6). The biomolecular corona that forms after exposure to biological fluids also dictates the interaction of nanoparticles with immune cells, tissues, their therapeutic activity and safety (7). The stability, immune recognition, cellular uptake and tissue specificity of nanoparticles can be further modulated by surface modification with polymers like polyethylene glycol (PEG), targeting ligands, peptides, antibodies, or other biomolecules (8).

Nanoparticles for pharmaceutical applications are broadly classified into three major categories: organic, inorganic, and carbon-based (9). Organic nanoparticles are derived from biological or synthetic macromolecules, while inorganic nanoparticles are synthesized from metals, metal oxides, or their salts (10). Carbon-based nanoparticles include graphene and carbon nanotubes. Several nanoplatfroms have been developed and characterized for biomedical applications. The selection of an appropriate nanoplatfrom depends on the physicochemical characteristics of the therapeutic payload, the intended route of administration, target tissue, desired release kinetics, and safety profile (11). Nanocarriers may also protect labile drugs from enzymatic degradation, improve aqueous dispersibility of poorly soluble compounds, and facilitate co-delivery of multiple therapeutic agents (12). The major nanoplatfroms investigated for rheumatoid arthritis therapy, including their composition, therapeutic cargo, and potential advantages, are summarized in Table I.

These properties are especially important in inflammatory diseases like RA, where systemic administration of conventional anti-inflammatory and disease modifying drugs may be associated with poor tissue specificity, rapid clearance, poor solubility, and dose limiting systemic side effects (27). Nanotechnology thus offers a chance to alter the pharmacokinetics and biodistribution of drugs to enhance the accumulation of drugs in inflamed joints (28). The inflamed rheumatoid joint has increased vascular permeability, activated endothelial cells, synovial hyperplasia, infiltration of immune cells, increased levels of inflammatory cytokines, oxidative stress, and increased activity of proteolytic enzymes (29). These pathological features can serve as endogenous biological signals that can be used for targeted or stimuli-responsive nanoparticle delivery.

Table I. Classification, composition, therapeutic cargo, experimental evidence, and outcomes of nanocarriers used for rheumatoid arthritis therapy

Nanocarrier type	Representative materials/composition	Therapeutic cargo (active ingredient)	Type of study investigated	Main findings (with quantitative data where available)	Potential advantages in RA	Ref.
Liposomes	Phospholipid/cholesterol vesicles; PEGylated and ligand-functionalized liposomes	Methotrexate, corticosteroids, NSAIDs, curcumin, siRNA	<i>In vitro</i> , <i>in vivo</i> (animal models), and/or clinical studies	Enhanced drug accumulation in inflamed joints, improved pharmacokinetic profile, reduced systemic exposure compared with free drugs; specific quantitative outcomes reported in individual studies	High biocompatibility; improved pharmacokinetics; enhanced accumulation in inflamed joints; reduced systemic toxicity	13
Polymeric nanoparticles	PLGA, PLA, PCL, chitosan, PEG-based polymers	Methotrexate, corticosteroids, curcumin, celestrol, siRNA/miRNA	<i>In vitro</i> and <i>in vivo</i> RA models	Improved drug stability, prolonged circulation time, enhanced anti-inflammatory effects, and reduction of inflammatory cytokines compared with free drug formulations	Improved drug stability and bioavailability; prolonged exposure; reduced dosing frequency	14
Polymeric micelles	PEG-PLA, PEG-PCL and other amphiphilic block copolymers	Curcumin, celestrol, NSAIDs, hydrophobic drugs	<i>In vitro</i> and <i>in vivo</i> studies	Improved solubility and cellular uptake of poorly soluble compounds with enhanced therapeutic response	Enhanced solubility and bioavailability; small size; improved tissue penetration	14
Dendrimers	PAMAM and other highly branched polymers	Methotrexate, NSAIDs, corticosteroids, nucleic acids	<i>In vitro</i> and <i>in vivo</i> studies	Efficient drug loading and targeted delivery due to multivalent surface functionality; reduced inflammatory responses in experimental models	High functional-group density; controlled drug loading; versatile surface engineering	15
Nanogels	Chitosan, hyaluronic acid, PEG and other hydrophilic polymers	Methotrexate, corticosteroids, proteins, nucleic acids	<i>In vitro</i> and <i>in vivo</i> studies	Sustained drug release and prolonged retention at inflammatory sites; improved local therapeutic effects	High loading capacity; prolonged retention; good biocompatibility; suitability for local administration	16
Solid lipid nanoparticles (SLNs)	Physiological solid lipids and surfactants	Methotrexate, corticosteroids, curcumin, NSAIDs	<i>In vitro</i> and <i>in vivo</i> studies	Improved drug protection and controlled release with enhanced stability compared with conventional formulations	Biocompatibility; physical stability; controlled release; improved drug protection	17
Nanostructured lipid carriers (NLCs)	Mixtures of solid and liquid lipids	Curcumin, corticosteroids, NSAIDs and hydrophobic drugs	<i>In vitro</i> and <i>in vivo</i> studies	Higher drug-loading capacity and improved stability compared with SLNs	Higher loading capacity than SLNs; improved stability and bioavailability	18

Mesoporous silica nanoparticles	Functionalized mesoporous silica	Small molecules, proteins, nucleic acids	<i>In vitro</i> and <i>in vivo</i> studies	High cargo capacity with tunable surface modification enabling targeted and theranostic applications	High cargo capacity; versatile surface modification; targeted and theranostic potential	19
Gold nanoparticles	Functionalized gold nanoparticles and nanostructures	Small molecules, nucleic acids, therapeutic agents	<i>In vitro</i> and <i>in vivo</i> studies	Modulation of inflammatory pathways and potential application in targeted delivery and imaging	Targeted delivery; imaging capability; therapeutic and theranostic potential	20
Iron oxide nanoparticles	Superparamagnetic iron oxide nanoparticles (SPIONs)	Drugs, proteins, nucleic acids	<i>In vitro</i> and <i>in vivo</i> studies	Magnetic targeting capability and MRI-based tracking demonstrated in experimental models	Magnetic targeting; MRI compatibility; theranostic potential	21
Protein-based nanoparticles	Albumin, ferritin and other protein-based systems	Hydrophobic drugs, proteins, nucleic acids	<i>In vitro</i> and <i>in vivo</i> studies	Improved biological compatibility and efficient interaction with target cells	Biocompatibility; biodegradability; efficient biological interaction	22
Exosome/extracellular vesicle nanocarriers	MSC-derived and engineered extracellular vesicles	miRNAs, siRNAs, proteins, small molecules	<i>In vitro</i> and <i>in vivo</i> studies	Efficient nucleic acid delivery and immunomodulatory effects demonstrated in inflammatory models	High biocompatibility; efficient nucleic acid delivery; intrinsic immunomodulatory properties	23
Hybrid nanocarriers	Lipid-polymer, lipid-inorganic, polymer-inorganic systems	Drugs, nucleic acids, imaging agents	<i>In vitro</i> and <i>in vivo</i> studies	Combined advantages of multiple nanoplateforms, including improved stability and multifunctionality	Multifunctionality; improved stability; controlled release; simultaneous targeting and imaging	24
Stimuli-responsive nanoparticles	pH-, ROS-, enzyme-, redox-, and temperature-responsive systems	Methotrexate, corticosteroids, phytochemicals, nucleic acids	<i>In vitro</i> and <i>in vivo</i> studies	Triggered drug release under inflammatory conditions with reduced premature release and systemic exposure	Enhanced drug release within inflamed joints; reduced premature release and systemic exposure	25
Nanocomposite hydrogels	Hyaluronic acid, chitosan, PEG combined with nanoparticles	Methotrexate, corticosteroids, biologics, phytochemicals, nucleic acids	<i>In vitro</i> and <i>in vivo</i> studies	Prolonged joint retention and sustained release after local administration	Prolonged joint retention; localized treatment; reduced systemic exposure and administration frequency	26

CIA, collagen-induced arthritis; MRI, magnetic resonance imaging; MSC, mesenchymal stem cell; NLCs, nanostructured lipid carriers; NSAIDs, nonsteroidal anti-inflammatory drugs; PAMAM, polyamidoamine; PCL, polycaprolactone; PEG, polyethylene glycol; PLA, polylactic acid; PLGA, poly(lactic-co-glycolic acid); ROS, reactive oxygen species; SLNs, solid lipid nanoparticles; SPIONs, superparamagnetic iron oxide nanoparticles.

Nanoparticles can also interact with other cells that play a role in the pathogenesis of RA, such as macrophages, dendritic cells, neutrophils, fibroblast-like synoviocytes, and others (30). Thus, the use of nanocarriers for the delivery of conventional therapeutics, biological agents, nucleic acids, peptides, natural products, and combination therapies has been explored, with the goal of enhancing the local therapeutic exposure while minimizing the systemic drug burden (31). The principal molecular and cellular targets explored in nanotechnology-based RA therapies, together with representative nanocarrier systems, therapeutic strategies, and their proposed outcomes, are summarized in Table II.

Among the various nanotechnology-based delivery platforms investigated for RA, several major nanocarrier systems have demonstrated particular potential because of their distinct physicochemical properties, drug loading capacities, targeting capabilities, and controlled release characteristics. The principal features of these platforms are briefly described below:

Dendrimers. – Highly branched, three-dimensional synthetic macromolecules characterized by a well-defined hierarchical architecture, low cytotoxicity, high aqueous solubility, and multivalent surface functionality, making them suitable as drug delivery vehicles, diagnostic agents, and gene carriers (55).

Liposomes. – Spherical vesicles composed of one or more amphiphilic phospholipid bilayers enclosing an aqueous core, capable of encapsulating both hydrophilic and hydrophobic drugs, with well-established biocompatibility and versatility (56).

Polymeric nanocarriers. – Polymer based nanoparticles or nanomicelles that facilitate membrane traversal, enhanced cellular uptake, and controlled drug delivery. These systems can be engineered with stimuli responsive elements for pH, enzyme, or redox triggered drug release (57).

Stimuli-responsive nanoparticles. – Nanoparticles engineered to respond to specific endogenous or exogenous stimuli, including reactive oxygen species (ROS), pH gradients, matrix metalloproteinase (MMP) activity, or applied magnetic fields to enable precision drug release at the target site (58).

Hydrogels. – Three-dimensional, water-swollen polymeric networks with high biocompatibility, tunable mechanical properties, and porous architecture that permit sustained, controlled, and localized drug release; injectable hydrogels are particularly attractive for intra-articular administration (59).

Nanofibers represent another significant nanotechnology platform, with applications in wound dressing, antimicrobial treatment, and tissue diagnostics. Their biodegradability and targeted delivery capacity minimize collateral damage to healthy tissue (60–62). Drug delivery *via* amphiphilic nanoparticles has emerged as one of the most consequential applications: these carriers associate with the drug molecule through covalent conjugation or non-covalent encapsulation while remaining compatible with biological fluids, thereby improving bioavailability at target sites, prolonging drug half-life, and enabling dose reduction without compromising therapeutic efficacy (63). The present review focuses specifically on nanotechnology-based drug delivery systems for the treatment of rheumatoid arthritis, examining the mechanistic rationale for each platform and critically evaluating the evidence from preclinical and early clinical studies.

Table II. Molecular and cellular targets of nanotechnology-based therapeutic strategies for rheumatoid arthritis

Molecular/cellular target	Representative nanocarrier system	Representative therapeutic cargo/approach	Proposed mechanism	Potential therapeutic outcome	Ref.
NF- κ B signalling	Liposomes, polymeric nanoparticles, lipid nanoparticles	Curcumin, celastrol, methotrexate, corticosteroids	Inhibition of NF- κ B activation and nuclear translocation	Reduced TNF- α , IL-1 β , IL-6 production and synovial inflammation	32
NLRP3 inflammasome	Polymeric nanoparticles, lipid-based nanocarriers	Curcumin, NLRP3 inhibitors	Suppression of NLRP3 activation and caspase-1 signalling	Reduced IL-1 β /IL-18 production and inflammatory injury	33
JAK/STAT signalling	Liposomes, polymeric nanoparticles	JAK inhibitors, siRNA	Suppression of cytokine-induced JAK/STAT activation	Reduced inflammatory cytokine signalling	34
TNF- α signalling	Targeted nanoparticles, liposomes	Anti-TNF agents and TNF-modulating cargo	Local neutralization or inhibition of TNF- α activity	Reduced synovitis and joint destruction	35
IL-6/IL-6R signalling	Polymeric nanoparticles, liposomes	Anti-IL-6/IL-6R agents	Inhibition of IL-6-mediated signalling	Reduced inflammation and systemic inflammatory responses	(36)
MAPK signalling	Polymeric nanoparticles, lipid nanoparticles	Curcumin, celastrol	Modulation of ERK, JNK, and p38 signalling	Reduced inflammatory mediator production	(37)
PI3K/AKT/mTOR signalling	Nanoparticles and nanoformulated small molecules	Small-molecule inhibitors and natural compounds	Modulation of inflammatory cell activation, survival, and metabolism	Reduced inflammatory responses	(38)
TLR signalling	Liposomes, polymeric nanoparticles	TLR inhibitors and siRNA	Suppression of innate immune receptor signalling	Reduced downstream inflammatory cytokine production	(39)
Oxidative stress/ROS	Stimuli-responsive nanoparticles	Curcumin, resveratrol, quercetin	ROS scavenging and/or ROS-triggered drug release	Restoration of redox balance and reduced tissue injury	(40)
Nrf2/HO-1 pathway	Polymeric nanoparticles, lipid-based nanocarriers	Curcumin, resveratrol, and related compounds	Activation of endogenous antioxidant defense	Enhanced antioxidant protection and reduced inflammation	41
Macrophage modulation	Liposomes, polymeric nanoparticles, exosomes	Methotrexate, corticosteroids, siRNA, phytochemicals	Preferential uptake and modulation of macrophage activity	Reduced inflammatory macrophage activity and synovitis	42

M1 macrophage polarization	Nanoparticles and exosome-based systems	siRNA, miRNA modulators, curcumin	Suppression of pro-inflammatory macrophage polarization	Reduced TNF- α , IL-1 β , and IL-6 production	43
M2 macrophage polarization	Biomimetic nanoparticles, exosomes	Small molecules and gene-regulatory cargo	Promotion of reparative/immunoregulatory macrophage phenotype	Resolution of inflammation and tissue repair	44
Fibroblast-like synoviocytes (FLSs)	Polymeric nanoparticles, lipid nanoparticles	Methotrexate, siRNA, and miRNA modulators	Inhibition of proliferation, migration, and inflammatory activity	Reduced synovial hyperplasia and pannus formation	45
VEGF/angiogenesis	Targeted nanoparticles	VEGF-targeting agents and siRNA	Suppression of VEGF-mediated vascular proliferation	Reduced pathological angiogenesis	46
Osteoclastogenesis	Nanoparticles and lipid-based carriers	Bisphosphonates, siRNA, and antiresorptive agents	Inhibition of osteoclast differentiation and activity	Reduced bone erosion	47
RANK/RANKL signalling	Polymeric nanoparticles, lipid nanoparticles	RANKL modulators and siRNA	Suppression of RANKL-driven osteoclastogenesis	Reduced bone destruction	48, 49
COX-2/PGE2 pathway	Liposomes and polymeric nanoparticles	Celecoxib, diclofenac, and other NSAIDs	Inhibition of prostaglandin synthesis	Reduced pain, edema, and inflammation	50
miRNA dysregulation	Exosomes, lipid nanoparticles	miRNA mimics and antagonists	Restoration or inhibition of disease-associated miRNA networks	Regulation of inflammatory and pathogenic cellular behaviour	51
siRNA-mediated gene silencing	Lipid nanoparticles, polymeric nanoparticles	siRNA targeting inflammatory genes	Sequence-specific suppression of target gene expression	Selective inhibition of pathogenic pathways	52
Inflammatory microenvironment	Stimuli-responsive nanoparticles	Anti-inflammatory drugs, corticosteroids, and phytochemicals	Stimuli-triggered localized drug release	Enhanced drug release within inflamed joints and reduced systemic exposure	53
Joint/cartilage targeting	Ligand-functionalized nanoparticles	Methotrexate, corticosteroids, biologics, and nucleic acids	Receptor- or extracellular matrix-mediated accumulation	Increased local drug concentration and improved therapeutic efficacy	54

AKT, protein kinase B; COX-2, cyclooxygenase-2; ERK, extracellular signal-regulated kinase; FLSs, fibroblast-like synoviocytes; HO-1, heme oxygenase-1; IL, interleukin; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; miRNA, microRNA; mTOR, mechanistic target of rapamycin; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-like receptor family pyrin domain-containing 3; PI3K, phosphoinositide 3-kinase; RANK, receptor activator of nuclear factor κ B; RANKL, receptor activator of nuclear factor κ B ligand; ROS, reactive oxygen species; siRNA, small interfering RNA; TLR, Toll-like receptor; TNF- α , tumor necrosis factor- α ; VEGF, vascular endothelial growth factor.

This review offers a focused and integrated view by linking the design of nanocarriers, the disease-specific pathological mechanisms, molecular and cellular targets, and therapeutic outcomes, as opposed to previous review articles that have summarized individual nanocarrier systems, therapeutic cargos, or general applications of nanotechnology in rheumatoid arthritis. The present work focuses on recent developments of targeted and stimuli responsive nanotechnology-based approaches and their potential to address the major drawbacks of conventional RA therapies such as lack of specificity, systemic toxicity and inadequate drug accumulation at inflamed joints. Furthermore, this review uniquely discusses the relationship between nanoparticle physicochemical properties and their biological performance, offering a mechanistic understanding of how nanoplateforms can be optimized for precision treatment of rheumatoid arthritis. This review combines nanomaterial engineering, immunological pathways, and translational hurdles to offer a comprehensive framework for future development of clinically relevant nanotherapeutic strategies for RA management.

Rheumatoid arthritis: Pathophysiology and disease burden

Joints are anatomical junctions at which two bones articulate. Articular cartilage covers the bone surfaces facilitates smooth movement, and the synovial fluid secreted by the synovium reduces friction and provides joint lubrication (64, 65). Arthritis is a pathological condition characterized by joint swelling, pain, and progressive degradation of cartilage and periarticular bone (66, 67). Major arthritis subtypes include osteoarthritis (OA), rheumatoid arthritis (RA), psoriatic arthritis (PsA), and gout, each distinguished by distinct pathophysiological mechanisms and therapeutic requirements (68).

RA is a chronic systemic autoimmune disease in which dysregulated immune activation generates autoantibodies, principally rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs), that target synovial tissue, initiating a cascade of chronic inflammation, pannus formation, and progressive cartilage and bone erosion (69, 70). In contrast to OA, which predominantly affects specific weight bearing joints as a consequence of mechanical wear, RA involves multiple joints in a symmetric distribution and is driven by autoimmune mechanisms (71). Epidemiologically, RA affects approximately 0.5–1 % of the adult population in industrialized nations and approximately 1 % of the global population (72). The pathogenesis of RA is multifactorial, encompassing genetic susceptibility (particularly HLA-DRB1 alleles), environmental triggers (including smoking and periodontal infections), and immune dysregulation involving innate and adaptive immune effector mechanisms (73, 74).

Oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) generation and antioxidant defense capacity, contributes significantly to synovocyte activation, cartilage matrix degradation, and impairment of synovial lubricant function (75). Key cellular mediators include activated B lymphocytes (producing autoantibodies), CD4⁺ T helper cells (particularly Th1 and Th17 subsets), and synovial macrophages, whose aberrant activation perpetuates the inflammatory milieu (76). Pro-inflammatory cytokines, tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6) occupy central roles in RA pathogenesis and represent validated pharmacological targets (77). The clinical manifestations of RA extend beyond the musculoskeletal system. Chronic disease is associated with cardiovascular complications, interstitial lung disease, dermatological manifestations, and significant psychological comorbidities (78). Juvenile idio-

pathic arthritis, which includes polyarticular RF-positive subtype most closely resembling adult RA, is notably more prevalent in females (79).

The pathogenesis of RA is thought to consist of a preclinical stage in which genetic and environmental factors contribute to the loss of immune tolerance and the production of autoantibodies, followed by a clinically apparent synovitis stage (80). Neoantigens can be formed by post-translational modification of proteins, which can then be recognized by autoreactive immune cells, leading to the production of ACPA and the development of systemic autoimmunity (81). The process of systemic autoimmunity to clinically apparent arthritis is characterized by endothelial cell activation, recruitment of leukocytes to the synovium and progressive remodeling of the synovial microenvironment (82). The increased vascular permeability and angiogenesis also allow inflammatory cells to enter and maintain synovial inflammation (83). A schematic overview of the multistep pathogenesis of rheumatoid arthritis, from genetic and environmental predisposition to immune activation, synovial inflammation, joint destruction, and systemic complications, is presented in Fig. 1.

Conventional treatment of rheumatoid arthritis: Efficacy and limitations

The primary therapeutic objectives in RA management are the achievement of clinical remission or low disease activity, alleviation of pain and systemic inflammation, prevention of structural joint damage and functional disability (84). Treatment strategy is indi-

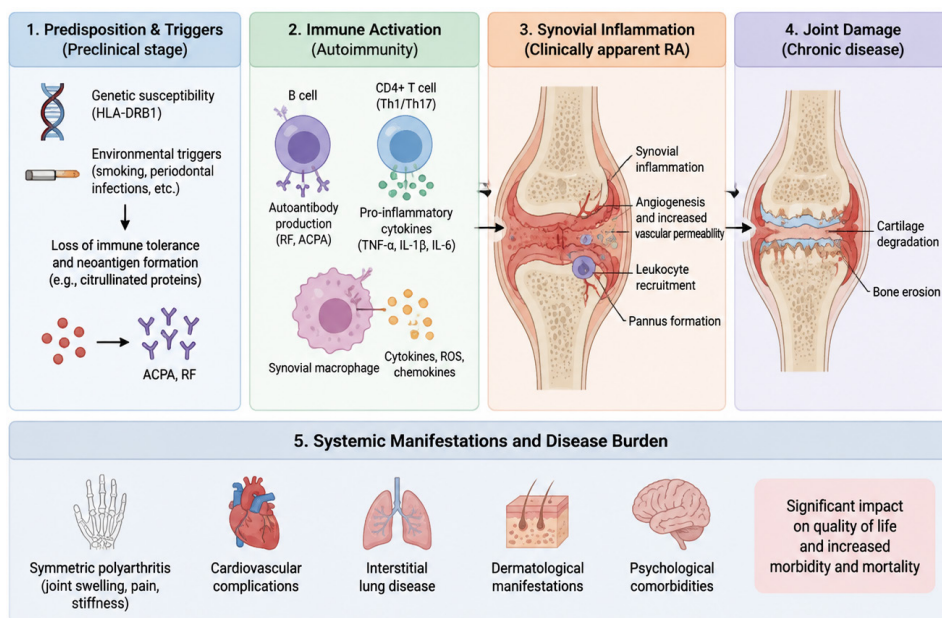


Fig. 1. Pathophysiological progression of RA. Schematic representation of RA development from genetic and environmental risk factors to immune activation, autoantibody production, and chronic synovial inflammation. Persistent inflammatory responses lead to pannus formation, cartilage degradation, and bone erosion, with systemic inflammation contributing to extra-articular complications and increased disease burden.

visualized according to disease activity, prognostic factors, comorbidities, and patient preferences (85, 86). Non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, ibuprofen, and naproxen constitute the mainstay of symptomatic relief through cyclooxygenase (COX) inhibition (87). Corticosteroids are used as bridging therapy and for short-term disease flare management. However, their prolonged use is associated with osteoporosis, hyperglycaemia, adrenal suppression, and increased infection susceptibility (88).

Disease modifying antirheumatic drugs (DMARDs) represent the cornerstone of RA therapy and are stratified into three classes (89). Conventional synthetic DMARDs (csDMARDs), including methotrexate (the anchor first-line therapy), leflunomide, sulfasalazine, and hydroxychloroquine slow disease progression through immunomodulatory mechanisms (90). Biological DMARDs (bDMARDs), including anti-TNF agents (etanercept, adalimumab, certolizumab pegol), anti-IL-6 receptor antibodies (tocilizumab), and B-cell depletion agents (rituximab), provide targeted cytokine blockade and have transformed RA management (91). Targeted synthetic DMARDs (tsDMARDs), specifically Janus kinase (JAK) inhibitors (tofacitinib, baricitinib, upadacitinib) have expanded the therapeutic armamentarium through oral administration and intracellular signalling blockade. Spleen tyrosine kinase (SYK) inhibitors represent additional investigational targets within this class (92). Despite their indispensable role, prolonged DMARD therapy is associated with adverse effects on cardiovascular, renal, hepatic, and gastrointestinal function, and up to 40 % of patients exhibit an inadequate or secondary loss of response (93). The risk of glucocorticoid-induced diabetes mellitus increases substantially with cumulative steroid exposure (94).

Conventional small molecule drugs are further limited by poor aqueous solubility, low bioavailability at the inflamed joint, and short plasma half-life, which restrict therapeutic utility and necessitate high systemic doses (95). Nanoparticle based drug delivery systems address these pharmacological shortcomings by enabling targeted delivery to inflamed joint tissues, substantially reducing the systemic drug burden, improving residence time at the therapeutic site, and enabling dose reduction (96). Through such targeted delivery, several conventional drugs previously marginalized due to systemic toxicity may potentially be rehabilitated for clinical use.

Barriers to nanomedicine delivery in rheumatoid arthritis

Despite considerable progress in the development of nanomedicines for RA, several biological and physicochemical barriers impede efficient targeted delivery to inflamed synovial tissue (97). The transport of nanoparticles in the rheumatoid joint microenvironment is affected by several interrelated factors such as particle size, shape, surface charge, hydrophilicity, mechanical properties, colloidal stability, and interactions with extracellular matrix components (98). In addition, the properties of inflamed synovium can differ depending on the stage of the disease, inflammatory activity, treatment status, and patient biology, which can lead to variable accumulation of nanoparticles and therapeutic effects (99).

Phagocytic clearance. – Non-targeted nanoparticles are susceptible to opsonization by complement proteins and immunoglobulins, followed by elimination by the mononuclear phagocyte system (MPS), reducing the circulating fraction available for joint accumulation (100).

Protein corona formation. – Adsorption of serum proteins onto nanoparticle surfaces alters their intended pharmacokinetic profile, reduces active targeting ligand accessibility, and promotes immunological recognition (101).

Insufficient systemic circulation time. – Adequate systemic exposure is required for nanoparticles to exploit the enhanced permeability and retention (EPR) effect at inflamed joints. Premature clearance by the MPS limits therapeutic accumulation (102).

Synovial fluid viscosity and cartilage barrier. – The viscoelastic synovial fluid and the dense extracellular matrix of avascular cartilage represent significant physicochemical barriers to nanoparticle diffusion and deep tissue penetration (103).

Endosomes (as a barrier). – For nucleic acid-based nanocarriers (siRNA, miRNA, plasmid DNA), escape from endosomal compartments following cellular internalization is critical. Failure to achieve endosomal escape results in lysosomal degradation of the nucleic acid payload before it can reach the cytoplasm or nucleus, rendering the formulation ineffective regardless of cellular uptake efficiency (104).

Cellular heterogeneity at the target site. – Variability in receptor expression and cell membrane composition across fibroblast like synoviocytes (FLS), macrophages, and chondrocytes may reduce consistent drug internalization (105).

Engineering strategies to overcome these limitations include surface modification with hydrophilic polymers, most commonly polyethylene glycol (PEG) to create a steric shield reducing protein adsorption and extending circulation half-life, as well as the incorporation of active targeting ligands (antibodies, peptides, aptamers, carbohydrate ligands) for site-specific recognition and internalization (106).

Nanotechnology based drug delivery systems for RA treatment

The prolonged use of conventional RA drugs is limited by systemic toxicity and inadequate joint bioavailability (107). Nanocarrier-based delivery systems address these limitations by encapsulating the active drug and directing it to the affected joint through passive or active targeting mechanisms (108). Passive targeting exploits the EPR effect at sites of synovial hypervascularity and impaired lymphatic drainage (109). Active targeting is predicated upon a specific molecular interaction between a surface functionalized nanocarrier and a cognate receptor overexpressed at the target site, concentrating the drug payload within a therapeutic window defined by maximum efficacy and minimum off-target toxicity (110). The following sections examine the major nanotechnology platforms investigated for RA treatment.

Macrophage-targeted nanocarriers

Synovial macrophages are preferentially targeted in RA nano-therapy because of their markedly elevated concentration at sites of inflammation and their central role in cytokine-mediated joint destruction (111). It has been reported that intra-articular injection of liposomes encapsulating clodronate, a bisphosphonate that induces macrophage apoptosis through intracellular ATP analogue accumulation in an experimental rabbit arthritis model produced significant transient reductions in synovial macrophage density and local inflammation (112). This proof-of-concept established the utility of intra-articular liposo-

mal delivery for selective macrophage depletion in RA synovium. Subsequent investigations have exploited the EPR effect in inflamed synovium, where hypervascularity and impaired lymphatic drainage facilitate the passive accumulation of nanocarriers (113). However, sequestration of non-targeted nanoparticles by macrophages in the reticuloendothelial system (RES) – particularly in the liver and spleen remains a significant limitation, reducing the fraction available for joint accumulation (114).

Polymeric nanocarriers and liposomal formulations

Indomethacin, a potent non-selective COX inhibitor with established anti-inflammatory efficacy but significant gastrointestinal and renal side effects, has been successfully encapsulated in both liposomal and lipid microsphere formulations for RA applications (115). Biodisposition studies in adjuvant-induced arthritic rats demonstrated that long-circulating liposomes of indomethacin produced superior pharmacokinetic profiles with enhanced joint accumulation relative to the free drug (116). PEGylation of indomethacin-loaded lipid microspheres further extended systemic circulation time and improved joint bioavailability (117). Encapsulation in Polysorbate 80-coated polymeric nano capsules demonstrated anti-inflammatory activity in experimental rat models with reduced gastrointestinal toxicity (118). Poly(amidoamine) (PAMAM) dendrimers have also been employed as carriers for indomethacin, demonstrating controlled site-specific release of this acidic anti-inflammatory drug (119).

Among glucocorticoids, PEG liposomal prednisolone with a markedly extended plasma half-life of approximately 50 hours compared to free prednisolone demonstrated complete remission of experimental arthritis when administered systemically, underscoring the dramatic pharmacokinetic benefit of nanoencapsulation (120). Dexamethasone has been successfully incorporated into diverse nanocarrier platforms. Heo and colleagues developed dextran sulfate nanoparticles as a theranostic nanomedicine platform for RA, demonstrating both therapeutic and imaging capabilities in preclinical models (121). Wang and colleagues demonstrated that targeted delivery of low-dose dexamethasone using PCL-PEG-PCL triblock copolymer micelles significantly reduced joint inflammation in collagen-induced arthritis (CIA) models while minimizing systemic glucocorticoid exposure (122). Liposome design parameters governing lipid composition, particle size, and surface engineering for drug delivery applications have been comprehensively reviewed in the literature (48, 123). Superparamagnetic PLGA microparticles loaded with dexamethasone have additionally been investigated for magnetically guided intra-articular administration, enabling sustained localized glucocorticoid release with spatiotemporal control (124).

Cytokine targeting nanoformulations

Given that dysregulated cytokine signalling is mechanistically central to RA pathogenesis, several nanoformulations have been designed to deliver cytokine-suppressive agents with improved joint specificity (125). Celastrol, a bioactive triterpenoid isolated from *Tripterygium wilfordii*, exhibits potent inhibitory activity against the NF- κ B and Notch1 signalling pathways (126). Celastrol-loaded nanomicelles have been shown to attenuate collagen-induced arthritis (CIA) through inhibition of these pathways, demonstrating significant joint protective effects in preclinical models (127). Chitosan, a natural biodegradable

polysaccharide with well-characterized mucosal adhesiveness and favorable biocompatibility, has been extensively employed as a nanocarrier matrix for cytokine-targeting formulations due to its cationic character, which facilitates cellular internalization (128).

Triptolide, a diterpenoid epoxide from *T. wilfordii* with potent immunosuppressive activity but a narrow therapeutic window due to hepatotoxicity, was conjugated with poly- γ -glutamic acid-grafted di-*tert*-butyl-L-aspartate hydrochloride nanoparticles, achieving nanoscale encapsulation that attenuated pro-inflammatory cytokine production in CIA models while improving the drug's physicochemical profile (129). Dextran sulfate-based amphiphilic nanomicelles functionalized with an MMP-2 enzyme-sensitive peptide linker (PVGLIG) and targeting the class A scavenger receptor (SR-A) overexpressed on activated macrophages (130). This dual-responsive system achieved conditional drug release specifically within the MMP rich synovial microenvironment, demonstrating significant short-term therapeutic efficacy in CIA models, though long-term safety data and comprehensive clinical validation remain outstanding (131). Additional macrophage-targeting strategies have employed folate receptors, galactose receptors, and mannose receptors as ligand receptor pairs for active nanocarrier targeting (132).

Receptor targeted nanoparticles

CD44, a transmembrane glycoprotein overexpressed on activated synovial macrophages, fibroblast like synoviocytes, and endothelial cells in RA, represents an important molecular target for active nanocarrier delivery (133). Hyaluronic acid (HA) binds CD44 with high affinity and selectivity. Accordingly, prednisolone encapsulated within HA-based nanoparticles has demonstrated effective CD44-mediated joint targeting and controlled drug delivery in preclinical RA models (134). Superparamagnetic iron oxide nanoparticles (SPIONs) loaded with dexamethasone enable both magnetically guided intra-articular delivery and MRI-based monitoring of nanocarrier distribution, exemplifying the theranostic potential of inorganic nanoparticles in RA management (135). Folate receptor- β (FR- β), overexpressed on activated macrophages but minimally expressed on resting cells, has been exploited for selective macrophage targeting through folic acid functionalized nanocarriers, providing a basis for macrophage-selective drug delivery with reduced off-target immunosuppression (136).

Gene therapy and nucleic acid based nanocarriers

Gene therapy for RA is designed to achieve durable disease modification at the molecular level by suppressing pro-inflammatory mediator expression (TNF- α , IL-1 β , IL-6) or upregulating endogenous anti-inflammatory regulators (IL-1Ra, IL-10, TGF- β) (137). Retroviral and adenoviral vector strategies for gene delivery to RA synovium. While viral vectors achieve high transduction efficiency, their clinical application has been constrained by immunogenicity, insertional mutagenesis risk, and manufacturing complexity, motivating the development of non-viral delivery alternatives (138).

Small interfering RNA (siRNA) complexed with cationic lipid nanoparticles (lipoplexes) has been used to silence TNF- α , IL-1, and IL-18 in experimental arthritis models, producing significant analgesic and anti-inflammatory effects (139). The principal limitation of lipoplexes is their susceptibility to serum protein mediated destabilization and

endosomal degradation, necessitating repeated administration (140). Chitosan/siRNA nanoparticles represent a more stable non-viral carrier system with inherently improved endosomal escape capability due to the proton sponge effect of chitosan's cationic amine groups. Effective TNF- α knockdown in peritoneal macrophages and significant disease attenuation in a murine CIA model (141). MicroRNA (miRNA)-based therapy has also emerged as a promising modality. Intra-articular injection of miR-15a, which targets Bcl-2 and promotes fibroblast-like synoviocyte (FLS) apoptosis – significantly reduced synovial hyperplasia in an autoantibody mediated murine arthritis model (142). Co-encapsulation of NF- κ B-targeted siRNA and methotrexate in a hybrid nanocarrier produced synergistic anti-inflammatory effects superior to either agent alone, providing mechanistic rationale for nucleic acid-drug combination nanoformulations in RA (143). iRGD peptide-functionalised echogenic liposomes co-loaded with MTX and indocyanine green (ICG) demonstrated near-infrared fluorescence imaging-guided focused ultrasound-mediated drug delivery to arthritic joints, a sophisticated multimodal theranostic platform integrating real-time imaging with spatially controlled drug delivery (144).

Metal and inorganic nanoparticles

Silver nanoparticles functionalized with folic acid have been designed for selective targeting of FR- β expressing synovial macrophages. Glutathione-mediated intracellular release of Ag⁺ ions in the reducing synovial microenvironment induces selective apoptosis of pro-inflammatory M1 macrophages and promotes polarization towards the anti-inflammatory M2 phenotype, attenuating joint inflammation without nonspecific cytotoxicity (145). Tuftsin-modified alginate nanoparticles loaded with IL-10 plasmid DNA have similarly demonstrated macrophage repolarization and suppression of pro-inflammatory cytokine activity in arthritic rodent models (146).

Gold nanoparticles (AuNPs) possess intrinsic anti-angiogenic properties demonstrated through inhibitory effects on VEGF-induced endothelial cell proliferation and tube formation, providing a mechanistic basis for their application against synovial neovascularisation in RA (147). Camptothecin loaded in sterically stabilized phospholipid micelles demonstrated disease modifying anti-arthritis activity at low doses, exploiting the anti-proliferative effects of camptothecin against hyperproliferating synoviocytes (148). α v β 3 integrin-targeted perfluorocarbon nanoparticles loaded with fumagillin validated anti-angiogenic nanotherapy by suppressing synovial angiogenesis and joint inflammation in experimental arthritis (149). The evidence for cerium oxide and iron oxide nanoparticles with ROS-scavenging properties, and gold half-shells loaded with MTX for combined chemo-photo-thermal therapy in RA (150). Tocilizumab conjugated to hyaluronate coated gold nanoparticles demonstrated significantly enhanced reduction of IL-6 receptor signalling and joint inflammation in arthritic mice compared to free tocilizumab, underscoring the pharmacokinetic and pharmacodynamic advantages of antibody nanoparticle conjugation (151).

Immune tolerance induction and hydrogel-based systems

An emerging and conceptually distinct therapeutic paradigm in RA nanomedicine involves re-education of the dysregulated immune system to restore antigen-specific tolerance, potentially enabling disease modification without chronic broad-spectrum immunosuppression (152). The mechanistic basis and clinical prospects of immune tolerance

induction in RA, highlighting its potential to address the root immunological cause of the disease (153). Heat shock protein (HSP)-based strategies, exploiting the immunomodulatory and tolerogenic properties of HSPs in inflammatory conditions have been proposed as candidates for tolerance-inducing nanomedicine (154). Hydrogel based nanocarrier systems represent a particularly suitable platform for intra-articular RA therapy, offering sustained localized drug release, mechanical compliance with joint tissue, and potential for cartilage tissue regeneration (155). Polymeric hydrogel platforms for controlled drug delivery in arthritis, demonstrating that injectable, thermoresponsive, photo-cross linkable hydrogels can achieve sustained release of NSAIDs, corticosteroids, and biological agents over days to weeks following a single intra-articular injection, thereby reducing systemic drug burden and injection frequency (156).

Future perspectives and translational challenges

Despite remarkable preclinical advances, the clinical translation of nanotechnology-based RA therapeutics faces multifaceted challenges that must be systematically addressed. Inter-patient variability in disease immunophenotype, genetic background,

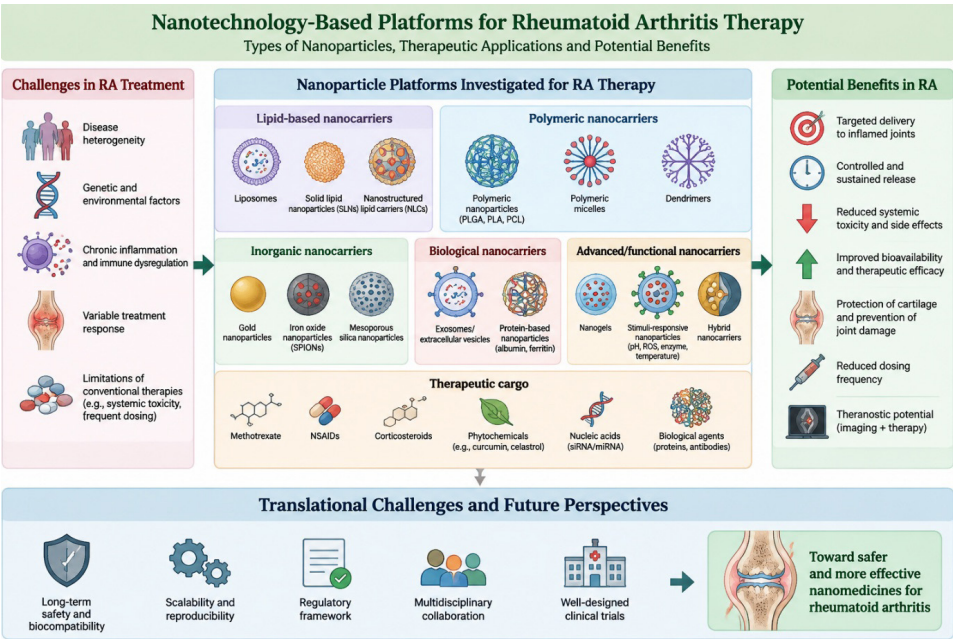


Fig. 2. Nanotechnology-based platforms for RA therapy: therapeutic applications, potential benefits, and translational challenges. Different nanotechnology-based approaches explored for the treatment of RA: exosome-based nanocarriers, biomimetic nanocarriers, stimuli-responsive nanoparticles, and combination nanotherapies. These nanoplatforms can be used to deliver drugs to specific sites, control drug release, minimize systemic side effects, and increase therapeutic efficacy by increasing the accumulation of drugs at inflamed joints. The figure also identifies key translation hurdles such as patient heterogeneity, long-term safety, scalability, regulatory issues, and better clinical translation of nanomedicine-based RA therapies.

and treatment history underscores the necessity for personalized nanomedicine strategies in which nanocarrier design and drug payload are tailored to individual patient immunological and molecular profiles. The development of theranostic nanoplatforms capable of simultaneous real-time diagnostic imaging and targeted therapy represents a promising avenue for treatment personalization and monitoring. Near-infrared fluorescence imaging integrated with iRGD-modified echogenic liposomes, illustrates the feasibility of multimodal theranostic RA nanomedicine. The major nanoplatforms and key translational considerations for advancing RA nanomedicine from preclinical development toward clinical application are summarized in Fig. 2.

Several emerging platforms merit priority attention for future development. First, exosome-based delivery systems, biological extracellular vesicles derived from mesenchymal stem cells or immune cells demonstrate intrinsic anti-inflammatory properties and the capacity to traverse biological barriers that limit synthetic nanoparticles, offering a biomimetic delivery alternative with low immunogenicity and natural cell-homing mechanisms. Second, biomimetic nanocarriers engineered with cell membrane coatings derived from macrophages, neutrophils, or platelets exploit natural cell-homing signals for precision synovial targeting, combining the biocompatibility of biological membranes with the drug loading versatility of synthetic nanoparticles. Third, ROS responsive and pH-responsive nanocarriers that release their payload specifically in response to the oxidative and acidic microenvironment of inflamed RA synovium represent a highly selective stimulatory-responsive strategy well-matched to the pathophysiological features of RA, as characterized in the reactive oxygen species landscape of the inflamed joint. Fourth, combination nano therapy platforms co-delivering immunosuppressive drugs with siRNA or miRNA targeting key inflammatory signalling nodes have demonstrated synergistic efficacy in preclinical models and provide a compelling rationale for clinical development.

Long-term safety data remain unavailable for several otherwise promising formulations, including celastrol-based nanomicelles, silver nanoparticle systems, and certain viral gene therapy vectors. The scalability and batch-to-batch reproducibility of complex nanoformulations, the establishment of robust regulatory frameworks for nanomedicine approval, and the development of standardized characterization, biocompatibility testing, and toxicology requirements represent critical translational barriers. A multidisciplinary framework integrating pharmaceutical sciences, immunology, molecular biology, biomedical engineering, rheumatology, and clinical pharmacology is essential for the rigorous validation and safe clinical deployment of next generation RA nanomedicines.

While many nanotechnology-based RA therapies have shown promising results, most of the reported studies are still at the preclinical level, and the evidence is mostly based on *in vitro* cellular models and *in vivo* animal models like collagen-induced arthritis (CIA) and other experimental RA models. Clinical translation is still limited and only a few nanomedicine formulations have advanced to human studies. At present, there is no specific approval of a routine clinical use of a nanoparticle-based therapy for rheumatoid arthritis, and long-term safety, pharmacokinetics, manufacturing scalability, and regulatory compliance need to be evaluated.

CONCLUSIONS

The application of nanotechnology to rheumatoid arthritis therapeutics has demonstrated substantial potential for achieving targeted drug delivery with reduced systemic

toxicity, optimized joint bioavailability, and extended therapeutic windows. These properties have enabled the re-evaluation of several conventional pharmacological agents previously marginalized due to unacceptable systemic adverse effects. The nanotechnology platforms reviewed spanning liposomes, polymeric nanoparticles, dendrimers, metal and inorganic nanoparticles, hydrogels, nucleic acid-based carriers, and stimuli-responsive systems have each demonstrated meaningful efficacy in experimental arthritis models and, in select cases, early-phase clinical investigations. Mechanistically targeted approaches encompassing macrophage modulation, cytokine suppression, synovial angiogenesis inhibition, nucleic acid-mediated gene silencing, receptor-targeted delivery, and immune tolerance induction have collectively advanced the therapeutic landscape of RA. The field is progressing toward increasingly sophisticated platforms integrating simultaneous diagnostic and therapeutic capabilities, biomimetic targeting, and personalized drug-carrier design. Realizing the full clinical benefit of these platforms requires sustained collaborative investment among pharmacologists, molecular biologists, rheumatologists, biomedical engineers, and clinical specialists, with rigorous attention to translational barriers, long-term safety assessment, and regulatory pathway navigation.

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