REVIEW article

Targeted nano-constructs for the treatment of autoimmune diseases: A comprehensive review of advances, mechanisms, and clinical potential

Ramdas Bhat [1] * and **Sinchana S Bhat** [2]

[1] Srinivas College of Pharmacy, Valachil, Farangipete Post, Mangalore, Karnataka, India
[2] UG Student, Srinivas College of Pharmacy, Valachil, Farangipete Post, Mangalore, Karnataka, India
* Author to whom correspondence should be addressed

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Abstract: Autoimmune diseases are chronic, disabling disorders that involve immune system dysfunction and recognition of self-antigens and lead to progressive tissue injury. Afflecting about 5.0-10.0% of the world's population. Autoimmune diseases like rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, and type 1 diabetes are a major health burden. Traditional treatments, such as corticosteroids, disease-modifying antirheumatic drugs, and biologics, are not antigen-specific and have systemic immune suppression, incomplete remission, and chronic side effects. Targeted nanoconstructs, which involve nanoparticles designed for the targeted delivery of therapeutic agents, represent a revolutionary strategy through the amplification of bioavailability, optimization of immune modulation, and reduction of off-target toxicity. These nanosystems can deliver autoantigens or immunosuppressive drugs to target immune cells or tissues, thus restoring tolerance and suppressing inflammation. Here, we give a broad overview of nanoconstruct-based approaches for treating autoimmune diseases in this review. This review describes the design principles behind nanoconstructs, including surface functionalization, materials, and routes of delivery, and reviews how these constructs regulate innate and adaptive immune responses. In addition, it emphasizes recent clinical uses, illustrated with examples from rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, and type 1 diabetes, and discusses essential translational issues such as safety, scalability, regulatory hurdles, and disease heterogeneity. It is also discussing emerging trends in personalized nanomedicine, theranostics, and artificial intelligence-guided design. Together, these technologies poistion nanoconstructs as a promising next-generation platform for the effective, targeted, and individualized treatment of autoimmune diseases.

Introduction

Autoimmune disorders (ADs) are greater than 80 diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), and type 1 diabetes (T1D), that afflecting 5.0-10.0% of the world's population [1, 2]. These conditions are caused by abnormal immune responses against self-antigens that cause chronic inflammation, tissue injury, and organ dysfunction [3, 4]. The worldwide healthcare burden of ADs is high, with over $100 billion in costs annually in the United States alone [3]. Genetic susceptibility, as HLA gene variants, environmental precipitants as infection, stress, and immune

dysregulation propel AD pathogenesis, making treatment difficult [5, 6]. Current treatments, such as corticosteroids, NSAIDs, and biologics such as anti-TNFα antibodies, are aimed at symptom management and immunosuppression [7, 8]. These, however, tend to induce systemic side effects in the form of heightened risk of infection, osteoporosis, and cardiovascular complications, and cannot induce remission in the long term [9, 10]. Biologics, though more specific, are costly and can become ineffective with the development of neutralizing antibodies [11]. Nanotechnology has the potential to provide a solution by using targeted nanoconstructs, including polymeric nanoparticles, liposomes, and inorganic nanoparticles, that deliver therapeutics to a site with high specificity [12, 13]. The systems utilize the properties of their nanoscale dimensions, surface functionalization, and controlled release to maximize drug bioavailability, diminish off-target effects, and influence immune responses [14]. This review integrates progress in nanoconstruct-based treatments of ADs in terms of their design, mechanisms, applications, challenges, and future directions.

Pathophysiology of ADs: ADs arise due to a failure in immune tolerance, where the defense mechanism of the body is unable to recognize self-versus non-self. Such a failure enables autoreactive T and B lymphocytes-usually deleted in immune development to live and become functional. These cells bypass immune regulatory checkpoints, and the resultant production of autoantibodies and pro-inflammatory cytokines ultimately results in the disruption of healthy tissue [15-17]. T lymphocytes have a fundamental role in autoimmune responses. Certain $CD4^+$ T-helper cells, and more specifically the Th1 and Th17 subtypes, are major pro-inflammatory mediators. Th1 cells produce interferon-gamma (IFN-γ), inducing macrophage activation and augmenting cell-mediated immunity, whereas Th17 cells produce interleukin-17, inducing neutrophil recruitment and chronic inflammation [18, 19]. $CD8^+$ cytotoxic T cells also play a role in autoimmunity through direct killing and destruction of host tissues, as evidenced in diseases like MS and T1D [20, 21]. B lymphocytes are responsible for autoimmunity by the release of autoantibodies. Once autoreactive, B cells mature into plasma cells that release antibodies against self-antigens. In SLE, for instance, anti-nuclear antibodies (ANAs) precipitate out as immune complexes that deposit in tissues and activate complement and sustain inflammation [22, 23].

Antigen-presenting cells (APCs) like dendritic cells (DCs) and macrophages play a vital role in the induction and perpetuation of autoimmune responses. They display self-antigens on major histocompatibility complex molecules and provide co-stimulatory signals to trigger naïve T cells [14]. They also produce pro-inflammatory cytokines that enhance the immune response further [24-26]. The cytokine network of ADs is highly dysregulated. Pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and IL-1β, are increased, facilitating the recruitment of immune cells and tissue damage. Anti-inflammatory cytokines like IL-10 and transforming growth factor-beta (TGF-β), which inhibit inflammation and induce immune tolerance, are typically lacking [27-29]. Every autoimmune condition also has tissue-specific hurdles that are a challenge to drug delivery. For example, MS has the blood-brain barrier limiting immune and therapeutic entry into the CNS; ongoing synovial inflammation during RA maintains joint damage; and β-cell destruction in T1D leads to irreversible insulin deficiency [30, 31]. In addition, genetic and environmental influences contribute to AD pathogenesis. Certain HLA alleles (e.g., HLA-DR3 and HLA-DR4) predispose, whereas environmental stimuli such as viral infections, food antigens, and gut microbiota dysbiosis, may trigger disease in genetically susceptible individuals. These multifactorial and disease-specific processes require targeted and individualized therapeutic approaches [32-34].

Mechanisms of immune modulation: Nanoconstructs mediate their immunomodulatory activities by a wide array of mechanisms, providing new avenues to target the underlying immune dysregulation in ADs. Depending on their design and payload, these carriers either inhibit hyperactive immune responses or induce antigen-specific tolerance.

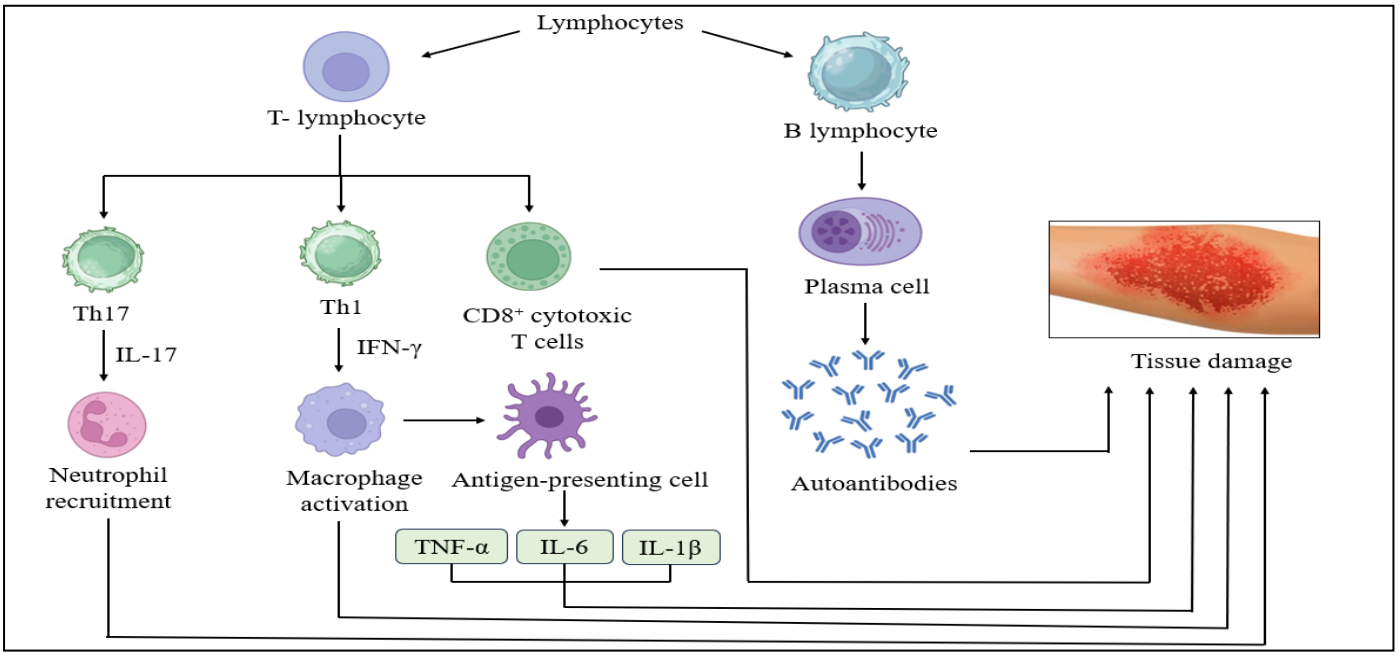

Figure 1: Pathophysiology of autoimmune diseases

Antigen-specific immune tolerance: One of the most hopeful strategies in autoimmune therapy is the induction of antigen-specific immune tolerance. Nanoparticles may be designed to transfer disease-specific autoantigens to APCs, for example, dendritic cells and macrophages, in a way that fosters tolerogenic instead of an immune response [35]. In experimental autoimmune encephalomyelitis (EAE), a model of MS in mice, poly-lactic-co-glycolic acid (PLG) nanoparticles encapsulating myelin peptides have been shown to induce T-cell anergy and amplify regulatory T cells (Tregs), subsequently arresting disease development [36]. Likewise, in SLE, CD22-targeted nanoparticles inactivate autoreactive B cells by selectively transferring tolerogenic signals or suppressive agents, resulting in long-term disease suppression [37].

Targeted drug delivery: Nanoconstructs improve therapeutic specificity by targeting immunosuppressive drugs to pathogenic immune cells or inflamed tissues. This minimizes systemic toxicity by far, which is a serious drawback of traditional immunosuppressants [38]. For example, chitosan nanocarriers were utilized for intranasal delivery of interferon-β in EAE models, which resulted in efficient central nervous system targeting and very low peripheral exposure. Likewise, liposomes loaded with methotrexate were functionalized to target synovial macrophages in RA, which increased drug retention within inflamed joints while decreasing systemic side effects [39, 40, 41].

Modulation of innate immunity: Aside from adaptive immunity, nanocarriers also can modulate the innate immune response, most notably by affecting macrophages and dendritic cells. The innate cells are key players in chronic inflammation. For instance, nanoparticles targeted to CD64 have been utilized to deliver anti-inflammatory mRNA molecules into SLE models, successfully reprogramming macrophages to a regulatory phenotype [42]. PEGylation-surface modification of the nanoparticle using polyethylene glycol-not only extends circulation time but also increases phagocytic cell uptake, improving delivery efficiency of anti-inflammatory drugs [43, 44].

Overcoming physiological barriers: Another significant limitation in the treatment of ADs is the existence of physiological barriers that limit drug entry to target tissues. Nanoparticles may be engineered to evade these barriers through surface modifications or size tuning. For instance, transferrin-functionalized nanoparticles were shown to cross the blood-brain barrier (BBB) and target remyelinating compounds onto CNS lesions in MS [45]. In RA, folate-conjugated nanoparticles were shown to preferentially accumulate in inflamed joints because of the overexpression of folate receptors [46, 47].

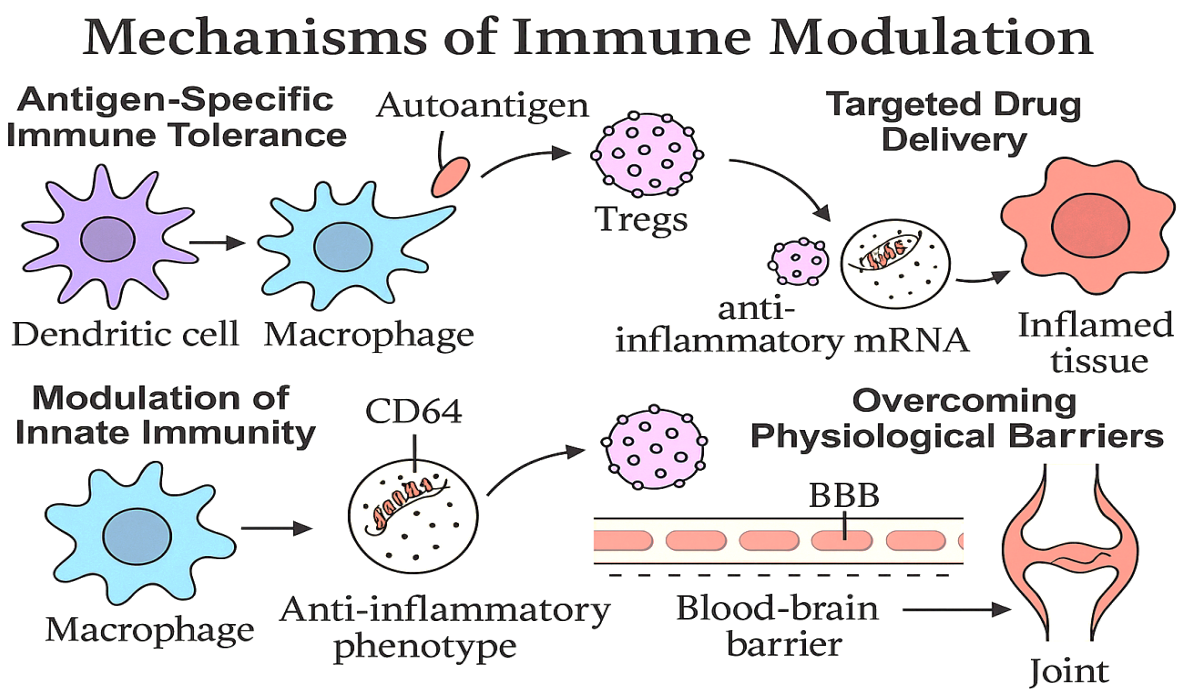

Figure 2: Mechanisms of immune modulation

Clinical applications: Nanotechnology-based treatments are being investigated in a number of large-scale autoimmune disorders, with numerous constructs showing potential in preclinical and clinical applications.

Multiple sclerosis: In MS, PLG nanoparticles carrying myelin antigens have exhibited potential to halt disease progression in EAE models through restoration of immune tolerance to CNS antigens [48]. Other nanoparticle-based strategies include liposomes carrying remyelinating agents to aid central nervous system repair and regeneration [49]. Celastrol-containing nanoparticles for sustained release and targeted CNS delivery are also under clinical evaluation and hold promise for better results in progressive MS [50].

Rheumatoid arthritis: Nanoconstructs have revolutionized RA treatment by allowing specific targeting of inflamed joint tissues. For example, nanoparticles conjugated with folate effectively deliver methotrexate to inflamed tissues, lowering systemic exposure and toxicity [51]. Additionally, Prussian blue nanoparticles, as they are magnetic in nature, provide real-time monitoring by MRI and theranostic potential in RA, with the ability to treat and monitor [52].

Systemic lupus erythematosus: In SLE, nanocarriers have two advantages of autoreactivity suppression and inflammation reduction. CD64-targeted nanoparticles were found to reduce systemic inflammation by targeting anti-inflammatory drugs directly at immune cells [53]. Gold nanoparticles with their good surface chemistry have been used to neutralize circulating autoantibodies and decrease immune complex deposition within organs [54].

Type 1 diabetes: In T1D, nanoparticle approaches try to prevent or postpone autoimmune destruction of β-cells in the pancreas. Nanoparticles that are anti-CD3 antibody-functionalized, like teplizumab, have been promising in regulating T-cell function and slowing disease progression [55]. Nanovaccines that carry insulin peptides have also been able to sustain β-cell function in models of early-stage T1D [56].

Other autoimmune diseases: Aside from the large ADs, nanotechnology is finding entry into several other diseases. For instance, oral nanoparticles composed of IL-10 mRNA are effective in restoring mucosal tolerance in IBD [57]. In dermatological autoimmune disease, topical drugs of cyclosporine-loaded nanoparticles have been shown to have increased penetration into the skin and decreased irritation in the management of psoriasis [58].

Challenges in clinical translation: Despite the promise of nanomedicine, several challenges hinder its widespread clinical application in autoimmune disorders.

Safety and toxicity: The chronic safety of nanomaterials is still a significant issue. Inorganic nanoparticles, e.g., gold or iron oxide nanoparticles, can deposit in the liver or spleen and, therefore, pose chronic toxicity concerns [59]. Though safer options like biodegradable nanoparticles made of PLG or chitosan are available, they also need to be optimized so that they do not inadvertently activate the immune response or cause off-target effects [60].

Scalability and manufacturing: Large-scale and reproducible production of nanoconstructs with reproducible physicochemical properties is still a bottleneck. Batch-to-batch heterogeneity in particle size, charge, and drug loading can hamper efficacy and safety [61]. Development in microfluidic technologies and automated platforms helps by facilitating high-throughput and controlled production of monodisperse nanoparticles [62].

Regulatory barriers: Regulatory authorities call for comprehensive characterization, such as pharmacokinetics, biodistribution, immunogenicity, and toxicity, before approval of nanoconstruct-based treatment. The stringent approach tends to lead to long approval times, particularly for sophisticated multifunctional systems [63, 64].

Disease heterogeneity: Autoimmune diseases are extremely heterogeneous, both between patients and within stages of disease development. Antigenic heterogeneity, heterogeneity in immune phenotypes, and heterogeneity in tissue involvement make it challenging to design a therapy that will fit all individuals [65]. There is a need for personalized therapies that take advantage of patient-specific biomarkers and immune signatures [66].

Immune evasion: Nanoparticles are seen and removed by the mononuclear phagocyte system, restricting their therapeutic window. To overcome this, stealth approaches, like PEGylation, zwitterionic coating, or biomimetic membranes, are being utilized to extend circulation and improve target specificity [67, 68].

Future directions: The potential for nanomedicine for autoimmune disorders lies in the creation of new materials and intelligent delivery systems. New generation nanocarriers are being designed with stimuli-responsive features that can respond to certain environmental stimuli like pH variations, redox potential, or the presence of inflammatory enzymes. Such systems enable targeted drug release at the inflammation site itself, thus minimizing systemic side effects and maximizing therapeutic efficiency. Concurrently, theranostic nanoplatforms are also rising as effective agents that integrate the treatment function with imaging properties, and this makes it possible to monitor inflammation and therapeutic responses in real time using modalities such as MRI. Personalization is the other pillar of significance in the development of autoimmune nanomedicine. Nanoconstructs can be tailored to an individual's immune profile or disease subtype using biomarker-driven methodologies. For example, nanoparticles can be filled with antigens, cytokines, or drugs based on a patient's specifically chosen HLA alleles or inflammatory profile. This specificity maximizes both safety and therapeutic effect. Further, the use of nanocarriers combined with advanced cellular therapies like CAR-T cells or adoptive regulatory T cells has promised to boost therapeutic impact. Nanoparticles have the potential to be integral in enhancing the survival, homing, and activity of such therapeutic cells. The future of nanomedicine will largely be determined by improvements in non-invasive delivery technologies and artificial intelligence. Channels such as intranasal and transdermal delivery are on the rise for their capacity to circumvent systemic degradation and target organs such as the brain or skin directly, both improving convenience as well as clinical effect. Meanwhile, artificial intelligence has the potential to transform the discipline with data-driven design and optimization of nanoconstructs. It can predict particle behavior, optimize material properties, and help stratify patients to identify the most likely candidates for nano-based therapies, opening the door for a new generation of precision and personalized autoimmune medicine [69].

Conclusion: Targeted nanoconstructs represent a paradigm shift in the treatment of autoimmune diseases, offering precision, reduced systemic toxicity, and the ability to restore immune balance in ways that conventional therapies often cannot achieve. From antigen-specific tolerance induction to site-directed delivery of immunosuppressive agents, nanomedicine provides a versatile and customizable platform tailored to the complex pathophysiology of multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and type 1 diabetes. Recent advances in nanoparticle engineering, encompassing material innovation, surface functionalization, and stimuli-responsive systems, have significantly enhanced their immunomodulatory capabilities and therapeutic efficacy. However, to fully realize the clinical potential of nanoconstructs, several hurdles must be addressed. Long-term safety profiles, large-scale manufacturing consistency, and regulatory clarity remain major barriers. The heterogeneity inherent in autoimmune diseases underscores the need for more personalized and biomarker-driven approaches. Looking forward, the integration of artificial intelligence for rational nanoconstruct design, the development of theranostic platforms for simultaneous therapy and monitoring, and the adoption of combination strategies with cell-based immunotherapies may further elevate the clinical impact of nanomedicine. As these innovations converge, targeted nanoconstructs are poised to become a cornerstone in the future management of autoimmune disorders, offering renewed hope for improved, durable outcomes for millions worldwide.

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