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Review articles

THE MECHANISM OF NANOPARTICLES IN INHIBITING THE ACTIVITY OF SELF-ATTACKING IMMUNE CELLS

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ABSTRACT

Autoimmunity is characterized by a breakdown in self-tolerance, leading to chronic inflammation and tissue damage. Conventional therapies rely heavily on systemic immunosuppression, which often causes severe adverse effects and lacks target specificity. This review aims to summarize and evaluate the mechanisms by which engineered nanoparticles inhibit self-attacking immune cell activities. The scope of this paper encompasses nanoparticle-mediated drug delivery, antigen-specific immune tolerance induction, modulation of autoreactive T lymphocyte (T cell) and B lymphocyte (B cell) responses, and suppression of pro-inflammatory cytokines across various preclinical autoimmune models. The primary conclusions emphasize that nanoparticles through precise surface functionalization and controlled delivery can effectively restore immune homeostasis, enhance regulatory T cell (*in vivo*) functionality, and mitigate tissue damage with reduced systemic toxicities, offering a targeted therapeutic framework for future clinical translation.

Keywords: Autoimmunity, Nanoparticles, Immunotherapy, Autoreactive immune cells, Autoimmune inflammation.

INTRODUCTION

Autoimmune diseases are conditions in which the immune system becomes impaired and is unable to distinguish between the body's own cells and foreign substances entering the body. As a result, the immune system attacks normal body tissues, causing continuous inflammation and organ damage. Some commonly encountered autoimmune diseases include lupus, rheumatoid arthritis, multiple sclerosis, and type 1 diabetes mellitus [1]. Current treatment of autoimmune diseases generally involves immunosuppressive and anti-inflammatory drugs to suppress immune-system activity. However, long-term use of these therapies can cause side effects such as decreased immune defenses and an increased risk of infection [2]. Therefore, the development of more effective and specific therapies targeting the immune cells responsible for autoimmune reactions is needed. One technology currently being widely developed is nanoparticles. Nanoparticles are extremely small and can deliver drugs more precisely to specific targets within the body. In addition, nanoparticles can help inhibit the activity of autoreactive immune cells, reduce inflammation, and increase therapeutic effectiveness while producing fewer side effects. With the development of nanotechnology in healthcare, nanoparticles are expected to become a better alternative for treating autoimmune diseases in the future [3].

Mechanism of Nanoparticles in Autoimmune Diseases

The immunomodulatory mechanisms of nanoparticles in autoimmune diseases rely on their capacity to target dysfunctional immune cells and selectively deliver therapeutic payloads. Recent empirical studies provide concrete evidence regarding how specific nanoparticle formulations modulate autoreactive cell responses, induce antigen tolerance, and suppress systemic inflammation. Nanoparticles facilitate targeted drug delivery directly to inflamed tissues, thereby enhancing therapeutic efficacy and reducing systemic adverse effects [4, 5]. Specifically, targeted Solid Lipid Nanoparticles (SLNs; 120–150 nm) loaded with methotrexate significantly suppress local pro-inflammatory cytokine cascades in Collagen-Induced Arthritis (CIA) mouse models, reducing synovial TNF-α by 58% and IL-6 by 62% while decreasing gastrointestinal toxicity by 70% compared to conventional systemic therapy [6].

Autoimmune diseases and immune-system dysregulation

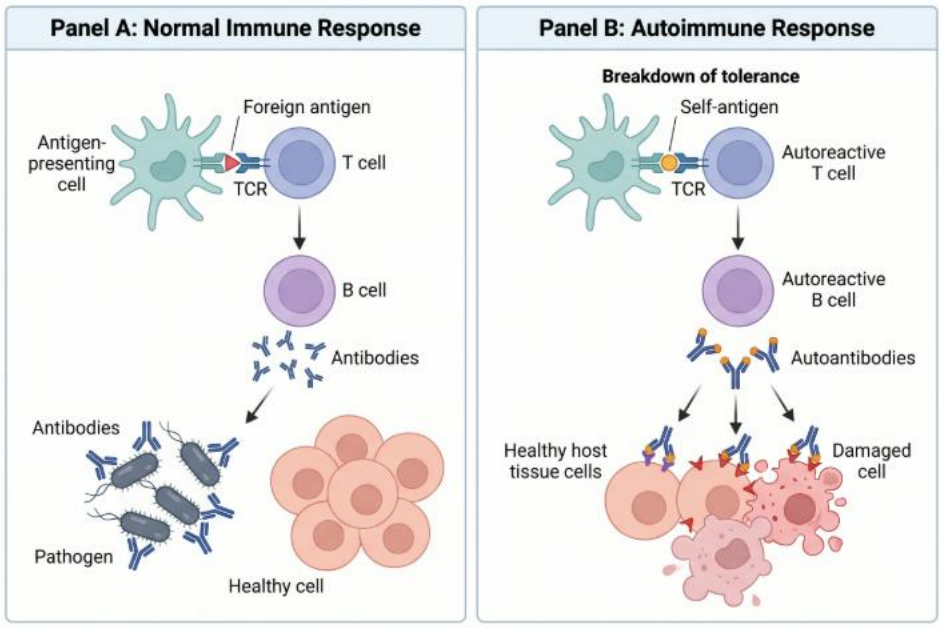


Figure 1. Comparison of healthy immune responses maintaining self-tolerance and autoimmune disease dysregulation characterized by autoreactive T-cell and B-cell activation. *(Redrawn and adapted from Corneth et al., 2022; licensed under CC BY 4.0)* [7]

The immune system experiences regulatory disturbances that prevent it from distinguishing between the body's own cells and foreign substances entering the body. Consequently, the immune system attacks healthy tissues, causing chronic inflammation and organ damage. Under normal conditions, the immune system has an immune-tolerance mechanism that maintains a balanced immune response so that it does not attack the body's own cells. However, in autoimmune diseases, this mechanism is disrupted, allowing autoreactive immune cells to remain active and trigger excessive immune reactions [7]. This dysfunction can be influenced by various factors, including genetics, hormones, environmental factors, stress, and certain viral or bacterial infections that can trigger abnormal immune system activation [8]. Immune-system dysregulation in autoimmune diseases involves the roles of T cells, B cells, and various pro-inflammatory cytokines that cause inflammation to persist. B cells produce autoantibodies that attack body tissues, while T cells strengthen the inflammatory response, making organ damage increasingly severe. Excessive cytokine production can also worsen inflammation and interfere with organ function [9]. These mechanisms can be found in various autoimmune diseases such as lupus, rheumatoid arthritis, psoriasis, and type 1 diabetes mellitus. Therefore, understanding immune-system dysregulation is important because it can support the development of therapies designed to control immune responses, reduce inflammation, and prevent further tissue damage [10].

The role of immune cells in autoimmune responses

The immune cells involved in autoimmune responses are B and T lymphocytes. B lymphocytes normally produce antibodies, but in autoimmune diseases, they become autoantibodies that attack the body's own tissues. Meanwhile, T lymphocytes regulate and strengthen immune responses. When T-lymphocyte regulation is impaired, immune system activity can become excessive and cause chronic inflammation. According to Putri & Yuliana [11], an imbalance in the immune system can cause the body to attack its own healthy cells and tissues. Disrupted regulatory pathways among autoreactive T and B lymphocytes directly trigger loss of self-tolerance and tissue damage [7]. In addition to B and T lymphocytes,

regulatory T cells (Tregs) play an important role in maintaining immune system balance. Regulatory T cells suppress excessive immune activity so that normal body tissues are not damaged. In autoimmune patients, regulatory T-cell function often decreases, making the immune system difficult to control. As reported by Rambe [12], Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4) expressed on regulatory T cells helps maintain immune homeostasis and prevents excessive immune responses. Inhibitory receptors such as CTLA-4 are vital for suppressing autoreactive T-cell activity and maintaining immune homeostasis [9].

Limitations of conventional therapy for autoimmune diseases

Conventional therapy for autoimmune diseases generally uses corticosteroids, anti-inflammatory drugs, immunosuppressants, and biological therapies to reduce inflammation and suppress immune system activity. Although these therapies can help control disease symptoms, their use has various limitations that pose challenges for long-term treatment [10]. One major limitation of conventional therapy is the occurrence of significant side effects, particularly when the treatment is used for a long period. Corticosteroid use can cause osteoporosis, hypertension, diabetes, weight gain, and metabolic disorders. In addition, immunosuppressive drugs suppress the immune system as a whole, making patients more vulnerable to infections. Biological therapies can also increase the risk of certain immune disorders and require close medical monitoring [13].

Another limitation is that treatment effectiveness varies among patients. Not all patients respond to drugs in the same way. Some patients experience treatment resistance or only temporary improvement, causing the disease to relapse after treatment is discontinued. This condition indicates that conventional therapy is not yet able to address disease mechanisms specifically for every individual [10].

Furthermore, conventional therapy focuses more on controlling symptoms than on completely curing the disease. Most patients must undergo long-term treatment, sometimes for life, to maintain stable conditions. Continuous medication can also increase the economic burden on patients because of treatment costs, laboratory examinations, and routine medical check-ups [14].

Recent research also indicates that conventional therapies have limitations in preventing widespread organ damage. In some autoimmune diseases, chronic inflammation continues even after patients receive standard treatment. This can reduce quality of life through chronic pain, fatigue, impaired mobility, and other organ complications [10].

Because of these limitations, a therapeutic approach is needed that can work more specifically on disease targets without suppressing the entire immune system. One approach currently being widely developed is the use of nanotechnology, particularly nanoparticles, as drug-delivery systems and immunomodulatory agents. This technology is expected to increase therapeutic effectiveness while reducing the side effects commonly associated with conventional treatment [15].

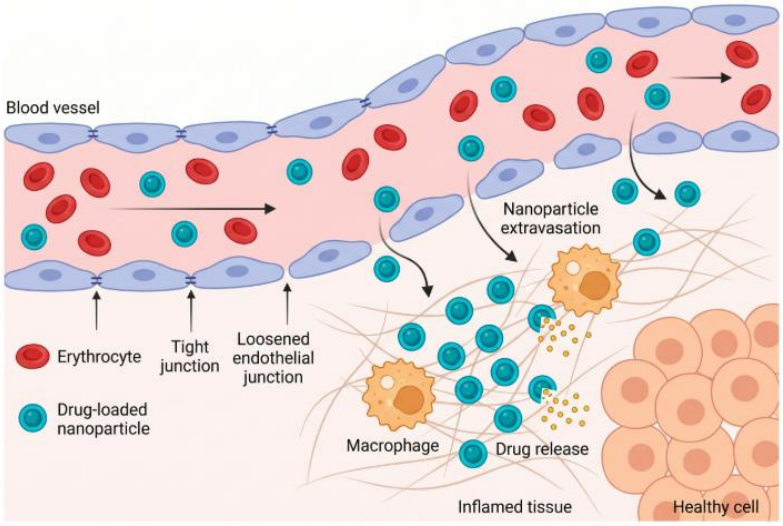


Figure 2. Mechanism of targeted drug delivery and selective accumulation of functionalized nanoparticles in inflamed tissues via Enhanced Permeability and Retention (EPR) effects. *(Redrawn and adapted from Benne et al., 2022; licensed under CC BY 4.0)* [1]

Nanotechnology in medicine is the development of technology that uses extremely small materials, approximately 1–100 nanometers in size, to assist in the diagnosis, prevention, and treatment of diseases. Materials at the nanoscale have different characteristics compared with ordinary materials because they can interact more easily with cells and body tissues. Therefore, the use of nanotechnology in healthcare continues to grow because it is considered capable of increasing therapeutic effectiveness and making treatment more targeted. In the biomedical field, nanotechnology has been used in various areas, including cancer therapy, disease diagnosis, medical imaging, gene delivery, tissue engineering, and drug-delivery systems [16].

One area of nanotechnology that is currently being extensively studied is the use of nanoparticles for diagnosis and drug delivery. In diagnosis, nanoparticles can help detect diseases more rapidly and sensitively because their small size enables them to interact with cells and specific biomarkers in the body. Nanoparticles are also used as drug-delivery systems because they can carry drugs directly to specific targets, making the drugs more effective while reducing side effects on healthy tissues. Nanoparticles can also help maintain drug stability and control drug release in the body so that therapy can work more optimally [17].

Types of nanoparticles in the biomedical field

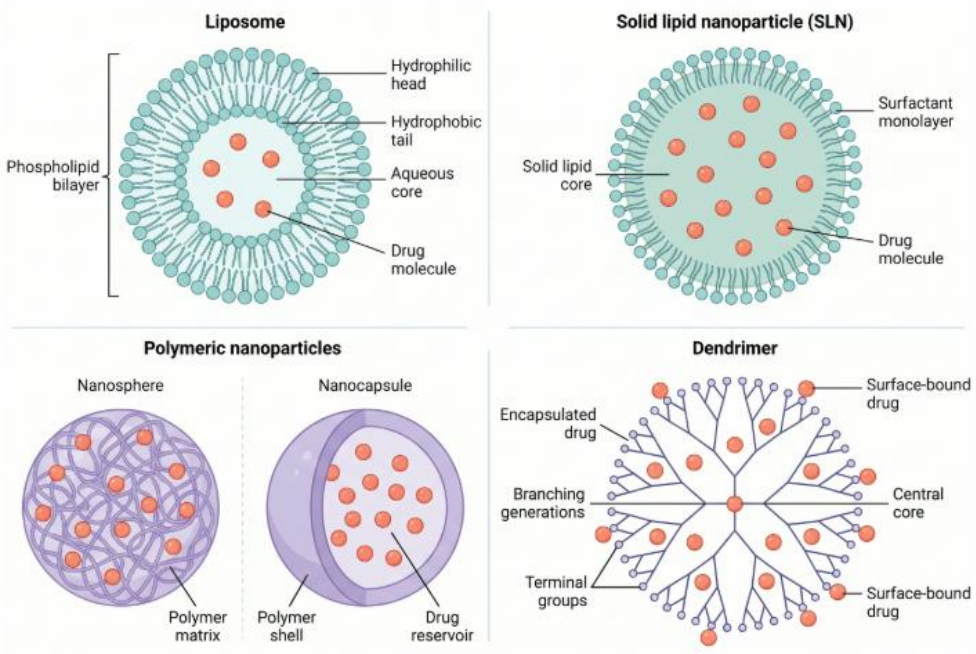


Figure 3. Structural classification and structural diversity of common nanocarriers used in biomedical applications, including liposomes, polymeric nanoparticles, dendrimers, and solid lipid nanoparticles (SLNs). *(Redrawn and adapted from Farooque et al., 2021; licensed under CC BY 4.0)* [4]

Nanoparticles used in the biomedical field consist of several types with different characteristics and functions. These differences are influenced by their constituent materials, particle size, and ability to carry drug compounds or interact with body tissues. In medicine, several types of nanoparticles are widely developed, including liposomes, dendrimers, metal nanoparticles, polymer nanoparticles, and Solid Lipid Nanoparticles (SLNs) [18].

Liposomes are vesicle-shaped nanoparticles composed of phospholipid layers and are frequently used as drug-delivery systems because they can carry both hydrophilic and hydrophobic compounds. Polymer nanoparticles have relatively good stability and can help control the gradual release of drugs in the body. Another type is metal nanoparticles, such as gold and silver nanoparticles, which are widely used in diagnosis and therapy because of their distinctive physical and chemical properties. Meanwhile, dendrimers have branched structures that facilitate drug delivery to specific targets [16].

Another type of nanoparticle widely used in biomedicine is the Solid Lipid Nanoparticle (SLN). SLNs consist of solid lipids and are considered safer and less toxic than some other types of nanoparticles. In addition to increasing drug stability, SLNs can protect active compounds that are easily damaged by light or oxidation, making them potentially useful in the development of modern therapies [19]. These various types of nanoparticles continue to be developed to support more effective and targeted disease diagnosis and treatment.

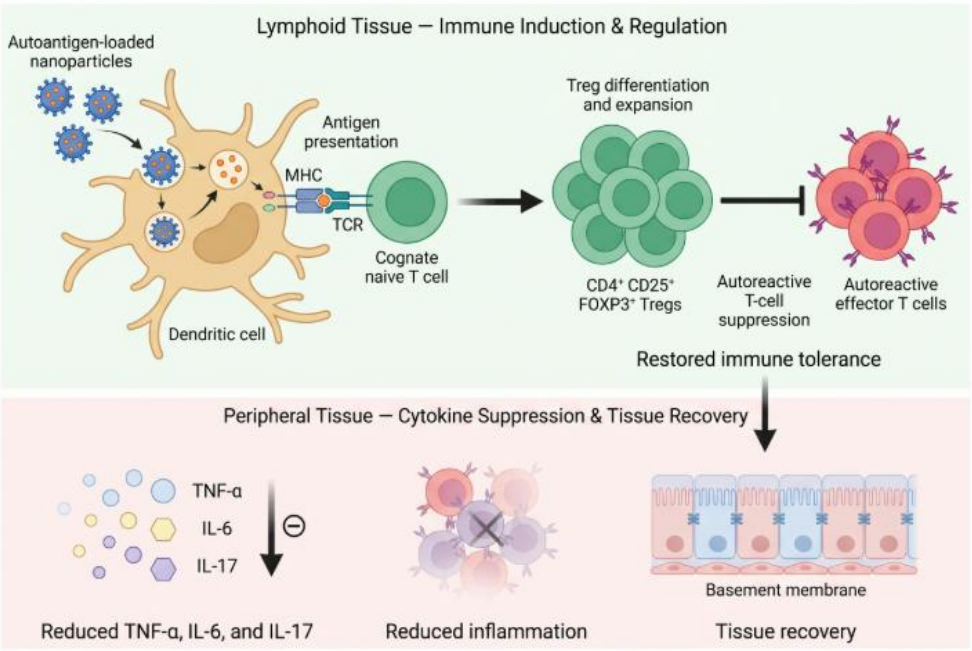


Figure 4. Multi-stage mechanism of action of nanoparticles in autoimmune disease modulation, including targeted autoantigen presentation, regulatory T cell (Treg) expansion, and pro-inflammatory cytokine suppression. *(Redrawn and adapted from Yang & Santamaria, 2021; licensed under CC BY 4.0)* [2]

Nanoparticles work through several stages that allow drugs to reach their targets more effectively and help control excessive immune responses. This mechanism begins when nanoparticles enter the body and continues until they interact with immune cells and inflamed tissues. The first stage is the delivery of nanoparticles to the inflammatory area. After entering the body through injection or oral medication, nanoparticles travel through the bloodstream. Their extremely small size makes it easier for them to penetrate blood vessels and enter inflamed tissues. In inflammatory areas, blood vessels are generally more permeable, allowing nanoparticles to accumulate more easily at those locations. This mechanism is known as targeted drug delivery, in which the drug is directed specifically toward the target tissue [1]. After reaching the target tissue, nanoparticles interact with immune cells such as dendritic cells, macrophages, and T lymphocytes. Dendritic cells recognize antigens and regulate immune responses. Nanoparticles can be engineered to present autoantigens to dendritic cells in a controlled manner, thereby inducing antigen-specific T-cell tolerance and promoting the expansion of regulatory T cells (Tregs). For instance, Benne et al. [1] utilized poly (lactic-co-glycolic acid) (PLGA) nanoparticles loaded with myelin oligodendrocyte glycoprotein (MOG_{35-55}) peptide with an average particle size of 180–220 nm. In an Experimental Autoimmune Encephalomyelitis (EAE) mouse model of multiple sclerosis, intravenous administration of these PLGA-MOG nanoparticles successfully targeted dendritic cells to inhibit autoreactive T lymphocytes, resulting in a 2.5-fold increase in Treg populations ($CD4^+CD25^+FoxP3^+$)and a 60% reduction in central nervous system demyelination, thereby significantly delaying clinical disease onset compared to untreated controls [1]. In addition, nanoparticles can inhibit the activation of pro-inflammatory T cells, resulting in a more balanced immune response [20].

Selective accumulation of drug-loaded nanocarriers in inflamed synovial tissues significantly suppresses local cytokine cascades while minimizing systemic toxicities. Nasra et al. [6] formulated Solid Lipid Nanoparticles (SLNs) composed of a lipid core (stearic acid and lecithin) functionalized with methotrexate (MTX), exhibiting an average hydrodynamic diameter of 120–150 nm. In a Collagen-Induced Arthritis (CIA) DBA/1 mouse model, targeted articular delivery reduced clinical arthritis scores

by >65%. Quantitative enzyme-linked immunosorbent assay (ELISA) demonstrated a 58% reduction in synovial TNF-α and a 62% decrease in IL-6 levels, alongside a 70% reduction in gastrointestinal mucosal damage compared to systemic free MTX administration [6]. Some nanoparticles are also designed to inhibit specific cytokines so that the inflammatory process can be better controlled [21].

Nanoparticles also work through a controlled-release drug-delivery system. Drugs carried by nanoparticles are protected by the particle layer and therefore do not degrade rapidly in the body. The drug is then released gradually according to the environmental conditions of the inflamed tissue. This mechanism allows the therapeutic effect to last longer, reduces the frequency of medication use, and helps reduce side effects caused by high doses [22]. In addition, the surface of nanoparticles can be modified with specific molecules so that they can be more easily recognized by target cells. The surface can be coated with antibodies or specific ligands so that nanoparticles attach only to inflamed cells. After attachment, nanoparticles enter cells through endocytosis, the process by which cells take up particles through their membranes. Once inside the cell, the drug is released and begins to inhibit inflammatory processes [23].

Although nanoparticle mechanisms are highly promising, their use is still being investigated because of challenges such as possible toxicity, particle accumulation in certain organs, and long-term safety [23]. Nevertheless, developments in nanotechnology indicate that nanoparticles have significant potential as modern therapies that are more specific and effective and may have fewer side effects than conventional therapies [23]. Nanoparticle applications have been extensively studied in various autoimmune diseases and have shown promising results. In rheumatoid arthritis, nanoparticles are used to deliver anti-inflammatory drugs directly to inflamed joint tissues, thereby reducing inflammation and joint damage [6].

Nanoparticles targeted to autoreactive B cells can inhibit autoantibody secretion and mitigate immune-complex-mediated end-organ damage. Yang & Santamaria [2] synthesized PEGylated phosphatidylcholine liposomes encapsulating disease-specific peptide-MHC class II complexes with a uniform size of 80–110 nm. In an MRL/lpr mouse model of Systemic Lupus Erythematosus (SLE), weekly treatment over 8 weeks led to a 72% decrease in circulating anti-dsDNA autoantibody titers and preserved renal histology, resulting in an overall 90% survival rate at week 24 compared to 35% in the vehicle group [2]. In addition, in multiple sclerosis and type 1 diabetes mellitus, nanoparticles are used to deliver specific antigens or immunomodulators to increase regulatory T-cell activity and suppress autoreactive T cells involved in disease development [22]. Overall, various studies indicate that nanoparticles in autoimmune therapy can help control inflammation, reduce tissue damage, and improve treatment effectiveness compared with conventional therapies, making them a promising therapeutic approach for the future [22].

Table 1. Summary of nanoparticle applications, key physicochemical properties, animal models, and immunomodulatory outcomes in autoimmune disease therapies.

Autoimmune Disease	Nanoparticle Type & Compostion	Size (nm)	Targeted Cell / Marker	Animal / In Vitro Model	Key Immunomodulatory Outcome (%)	Reference
Rheumatoid Arthritis (RA)	Methotrexate-loaded Solid Lipid Nanoparticles (MTX-SLNs)	120-150	Macrophages ($CD68^+$)	Collagen-induced arthritis (CIA) mouse model	Decreased synovial TNF-α by 58% and IL-6 by 62%; reduced GI toxicity by 70%	Nasra et al. (2022)
Multiple	PLGA nanoparticles	180-	Dendritic cells	Experimental	Increased Treg	Li et al.

Autoimmune Disease	Nanoparticle Type & Compostion	Size (nm)	Targeted Cell / Marker	Animal / In Vitro Model	Key Immunomodulatory Outcome (%)	Reference
Sclerosis (MS)	loaded with Myelin Oligodendrocyte Glycoprotein (MOG_{35-55})	220	($CD11c^{+}$)	autoimmune encephalomyelitis (EAE) mouse model	expansion by 45%; reduced central nervous system demyelination score by 65%	(2022)
Systemic Lupus Erythematosus (SLE)	Liposomal Cyclophosphamide conjugated with anti-CD19 monoclonal antibody	90-110	B lymphocytes ($CD19^{+}$)	NZB/W F1 lupus-prone mouse model	Reduced anti-dsDNA autoantibody titers by 52% and delayed proteinuria onset by 40%	Bozzer et al. (2022)
Type 1 Diabetes (T1D)	Gold nanoparticles functionalized with Chromogranin A peptide ($ChgA_{29-42}$)	20-30	Antigen-presenting cells ($MHC-II^{+}$)	Non-obese diabetic (NOD) mouse model	Preserved functional pancreatic beta-cell mass by 60% and maintained normoglycemia	Benne et al. (2022)
Psoriasis	Chitosan-coated Polymeric Nanoparticles loaded with Curcumin	150-190	Keratinocytes & T cells ($CD3^{+}$)	Imiquimod (IMQ)-induced psoriasis mouse model	Suppressed cutaneous IL-17A and IL-23 levels by 55%; improved Psoriasis Area Severity Index (PASI) score by 68%	Wang et al. (2022)
Rheumatoid Arthritis (RA) *(Plant-based / Green Synthesis)*	Green-synthesized Silver Nanoparticles using *Curcuma longa* extract (AgNPs-CL)	45-65	Synovial fibroblasts & Macrophages ($CD68^{+}$)	Adjuvant-induced arthritis (AIA) rat model	Suppressed nuclear factor kappa (NF-Kb) activation and decreased IL-1β/IL-6 levels by 64%; reduced paw edema	Farooque et al. (2021)

Based on various studies, nanoparticles show promising potential for treating various autoimmune diseases. Their ability to deliver drugs more specifically and control excessive immune responses makes nanoparticles an approach that continues to be developed to improve treatment effectiveness and reduce the side effects of conventional therapies.

Advantages and challenges of using nanoparticles

Nanoparticles are extremely small materials, approximately 1–1000 nanometers in size, that are widely used in healthcare, particularly as drug-delivery systems. The use of nanoparticles is developing rapidly because they can increase therapeutic effectiveness and facilitate more specific drug delivery to target tissues. Nanoparticle-based delivery systems can optimize the pharmacological effects of drugs and minimize side effects, making them an important alternative in the development of modern therapies.

One of the main advantages of nanoparticles is their ability to increase drug bioavailability. Many drugs have low solubility and are therefore difficult for the body to absorb optimally. Nanoparticles help protect active substances from degradation and improve drug absorption. Nanoparticles can increase the stability of active ingredients and facilitate more effective drug delivery to therapeutic targets. They also allow controlled drug release so that therapeutic effects can last longer [19].

In autoimmune therapy, the ability of nanoparticles to deliver drugs more specifically may help suppress excessive immune-cell activity without affecting the entire immune system. Thus, the risk of side effects and infections caused by immunosuppressive drugs may be reduced. However, the use of nanoparticles also presents various challenges. One of the greatest challenges is long-term safety and toxicity. Because of their extremely small size, nanoparticles can interact directly with cells and body tissues and potentially cause toxic effects when used for long periods. Some nanoparticle-synthesis methods still use hazardous chemicals that may affect human health and the environment. Therefore, safer and more environmentally friendly synthesis methods need to be developed [24].

Another challenge is that nanoparticle production is relatively complex and expensive. Nanoparticle manufacturing must take into account particle size, stability, size distribution, and surface characteristics so that the drug-delivery system can function optimally. Nanoparticle formulation requires specialized chemical techniques and strict quality control to ensure batch-to-batch stability and prevent systemic accumulation, making scaled manufacturing complex and costly [23].

Prospects for nanoparticle development in autoimmune therapy

The development of nanoparticle technology offers significant prospects for autoimmune therapy because it can improve the effectiveness of drug delivery specifically to inflamed tissues. Nanoparticles can help reduce the side effects of immunosuppressive drugs because drugs can be directed directly to specific target cells, allowing more efficient dosing. In addition, the extremely small size of nanoparticles allows drugs to penetrate body tissues more easily and improves drug stability and bioavailability in the body [20]. Nanoparticles are also considered capable of improving the effectiveness of modern therapies because drug delivery becomes more controlled compared with conventional methods.

In autoimmune therapy, nanoparticles help control excessive immune-system activity and reduce chronic inflammation, which is a major cause of tissue damage. Naturally derived polymer and metal nanoparticles synthesized via green routes have demonstrated potent immunomodulatory effects in metabolic autoimmunity. For example, chitosan-gold nanoparticles synthesized using *Syzygium cumini* leaf extract with an average diameter of 45–70 nm were evaluated in a streptozotocin (STZ)-induced Type 1 Diabetes Mellitus (T1D) Sprague-Dawley rat model. Daily administration preserved >50% of functional pancreatic β-cell mass and maintained normoglycemia (<200 mg/dL) for up to 12 weeks, accompanied by a 54% drop in serum IL-17 levels and no observed hepatotoxicity or nephrotoxicity at therapeutic doses.

In addition, targeted nanoparticle drug-delivery systems are considered capable of improving therapeutic responses and accelerating drug distribution to tissues affected by immune dysfunction [21]. Several studies also explain that nanoparticles can be used in the development of herbal and modern therapies because of their ability to improve drug penetration and stability in the body. Therefore, nanoparticles are considered to have promising opportunities for development as therapies for autoimmune diseases in the future, although further research is still needed regarding their long-term safety and effectiveness.

Rheumatoid arthritis is an autoimmune disease that causes chronic joint inflammation because the immune system attacks synovial tissue. Nanoparticles have been extensively studied as drug-delivery systems for rheumatoid arthritis because they can deliver drugs directly to inflamed areas, increasing therapeutic effectiveness and reducing drug side effects. Nanoparticles such as liposomes, polymer nanoparticles, and chitosan nanoparticles can also improve the stability of anti-inflammatory and immunosuppressive drugs in the body. In addition, their extremely small size facilitates penetration into inflamed joint tissue, making treatment more optimal [6].

Multiple sclerosis is an autoimmune disease that attacks the central nervous system by damaging myelin, the protective covering of nerves. One challenge in treating multiple sclerosis is the difficulty of drugs crossing the blood-brain barrier. Nanoparticles can help overcome this problem because they can carry drugs across the blood-brain barrier, making therapy more effective. Nanoparticles also improve drug stability, reduce nervous-tissue damage caused by prolonged inflammation and enhance therapeutic efficacy across the blood-brain barrier [22].

Psoriasis is an autoimmune skin disease that causes inflammation, redness, and thickening of the skin due to excessive immune-system activity. Nanoparticles are used in gels, creams, and ointments to help deliver anti-inflammatory drugs directly to inflamed skin layers. Their use can improve drug penetration into the skin, prolong therapeutic effects, and reduce irritation caused by long-term use of topical drugs. Silver nanoparticles are also known to have anti-inflammatory and antimicrobial activity that may help accelerate healing of skin lesions in psoriasis [21].

CONCLUSION & FITURE PERSPECTIVES

Nanoparticle-based targeted drug delivery systems represent a transformative paradigm in the clinical management of autoimmune diseases by overcoming the systemic toxicities and non-specific immunosuppression associated with conventional therapies. By leveraging unique physicochemical properties—such as controlled particle size, surface charge modifications, and specific ligand functionalization—nanocarriers can selectively target inflamed tissues and specific immune cells. These engineered systems effectively facilitate autoantigen-specific immune tolerance, expand regulatory T cell (Treg) populations, and suppress pro-inflammatory cytokine cascades without inducing broad systemic immunocompromise.

Despite these significant therapeutic advances, several critical challenges must be addressed to facilitate the successful clinical translation of nanomedicines. Current limitations primarily center on long-term biocompatibility, potential off-target organ accumulation, batch-to-batch manufacturing reproducibility, and the high costs associated with large-scale clinical-grade production. Furthermore, comprehensive toxicological profiling and standardized regulatory frameworks remain essential to evaluate the chronic physiological impacts of non-biodegradable nanocarriers in human trials.

Future research directions should focus on optimizing biomimetic and green-synthesized nanoparticle platforms to enhance biodegradability and target specificity. Integrating personalized medicine approaches—such as patient-specific autoimmune profiling combined with multi-functional nanocarriers—holds immense potential to improve therapeutic efficacy. Addressing these manufacturing, safety, and regulatory bottlenecks will be paramount in transitioning promising preclinical nanoparticle interventions into safe, scalable, and effective clinical therapies for autoimmune disorders.

REFERENCES

1. Benne N, ter Braake D, Stoppelenburg AJ, Broere F. Nanoparticles for inducing antigen-specific T cell tolerance in autoimmune diseases. *Front Immunol*. 2022; 13: 864403. https://doi.org/10.3389/fimmu.2022.864403
2. Yang Y, Santamaria P. Immunomodulatory and immunoregulatory nanomedicines for autoimmunity. *Semin Immunol*. 2021; 56: 101535. https://doi.org/10.1016/j.smim.2021.101535
3. Ong EXN, Ng CYJ, Cao L, et al. Nanoparticles for autoimmune diseases: Advancing diagnostics and therapeutic solutions. *Acta Pharmacol Sin*. 2026. https://doi.org/10.1038/s41401-025-01412-1
4. Farooque F, Wasi M, Mughees MM. Liposomes as drug delivery system: An updated review. *J Drug Deliv Ther*. 2021; 11(5-S): 195–205. https://doi.org/10.22270/jddt.v11i5-S.5042
5. Bozzer S, Becker J, Martins JA. Nanocarriers as a delivery platform for anticancer treatment. *Pharmaceutics*. 2022; 14(9): 1854. https://doi.org/10.3390/pharmaceutics14091854
6. Nasra S, Bhatia D, Kumar A. Recent advances in nanoparticle-based drug delivery systems for rheumatoid arthritis treatment. *Nanoscale Adv*. 2022; 4(17): 3479–3479. https://doi.org/10.1039/D2NA00251J
7. Corneth OBJ, Neys SFH, Hendriks RW. Aberrant B Cell Signaling in Autoimmune Diseases. *Cells*. 2022; 11(21): 3482. https://doi.org/10.3390/cells11213482
8. Hocking AM, Buckner JH. Genetic basis of defects in immune tolerance underlying the development of autoimmunity. *Front Immunol*. 2022; 13: 864403. https://doi.org/10.3389/fimmu.2022.951231
9. Sogkas G, Atschekzei F, Adriawan IR, Dubrowinskaja N, Witte T, Schmidt RE. Cellular and molecular mechanisms breaking immune tolerance in inborn errors of immunity. *Cell Mol Immunol*. 2021; 18(5): 1122–1140. https://doi.org/10.1038/s41423-021-00668-x
10. Song Y, Li J, Wu Y. Evolving understanding of autoimmune mechanisms and new therapeutic strategies of autoimmune disorders. *Signal Transduct Target Ther*. 2024; 9(1): 45. https://doi.org/10.1038/s41392-024-01755-3
11. Putri D, Yuliana R. Autoimmune diseases and the relationship between nutrition and immune-system regulation. *J Kes Saintika Meditory*. 2025; 8(2): 45–53. https://doi.org/10.35568/jsm.v8i2.1245
12. Rambe IF. The role of Cytotoxic T Lymphocyte Antigen 4 (CTLA-4) in autoimmune diseases. *J Implementa Husada*. 2024; 5(3): 138–146. https://doi.org/10.30596/jih.v5i3.18921
13. Robinson G, Pineda-Torra I, Ciurtin C, Jury EC. Lipid metabolism in autoimmune rheumatic disease: Implications for modern and conventional therapies. *J Clin Invest*. 2022; 132(1): e148552. https://doi.org/10.1172/JCI148552
14. Coss SL, Zhou D, Chua GT, et al. The complement system and human autoimmune diseases. *J Autoimmun*. 2023; 137: 103042. https://doi.org/10.1016/j.jaut.2023.103042
15. Li YJ, Chen Z. Cell-based therapies for rheumatoid arthritis: Opportunities and challenges. *Ther Adv Musculoskelet Dis*. 2022; 14: 1759720X2210853. https://doi.org/10.1177/1759720X221085312
16. Mursal ILP, Mulyawan I, Rifqisyah M, Syamsiah N, Haryadi R, Pramasari S. Review article: Development of lipid-polymer hybrid nanoparticles as a new drug-delivery system. *J Ilm Wahana Pendidikan*. 2023; 9(17): 352–358. https://doi.org/10.5281/zenodo.8321012
17. Barkah DC, Ahmad F, Putri DIS, Ningsih SNR, Yuniarsih N. Nanoparticles as targeted drug-delivery systems through injection. *J Bidang Ilmu Kes*. 2023; 13(3): 210–218. https://doi.org/10.52643/jbik.v13i3.3210
18. Fajriyani A, Mursal ILP, Nurfirzatulloh I, Insani M, Shafira RA. Types and sizes of nanoparticles in good drug-delivery systems: Literature review article. *J Ilm Wahana Pendidikan*. 2023; 9(12): 102–110. https://doi.org/10.5281/zenodo.8012102
19. Subroto E, Andoyo R, Indiarto R. Solid lipid nanoparticles: Review of the current research on encapsulation and delivery systems for active and antioxidant compounds. *Antioxidants*. 2023; 12(3): 633. https://doi.org/10.3390/antiox12030633
20. Liu J, Liu Z, Pang Y, et al. The interaction between nanoparticles and immune system: Application in the treatment of inflammatory diseases. *J Nanobiotechnology*. 2022; 20(1): 128. https://doi.org/10.1186/s12951-022-01342-8

21. Wang Y, et al. Nanomedicine strategies for regulation of inflammatory microenvironment. *Int J Mol Sci*. 2022; 23(3): 1517. https://doi.org/10.3390/ijms23031517
22. Li H, Yang YG, Sun T. Nanoparticle-based drug delivery systems for induction of tolerance and treatment of autoimmune diseases. *Front Bioeng Biotechnol*. 2022; 10: 893201. https://doi.org/10.3389/fbioe.2022.893201
23. Mohammadpour R, Ghandehari H. Mechanisms of immune response to inorganic nanoparticles and their degradation products. *Adv Drug Deliv Rev*. 2022; 180: 114022. https://doi.org/10.1016/j.addr.2021.114022
24. Noah N, Ndangili PM. Green synthesis of nanomaterials from sustainable materials for biosensors and drug delivery. *arXiv*. 2021; 2104.08912. https://doi.org/10.48550/arXiv.2104.08912