International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 18, Issue 1, 2026

Review Article

ADVANCED NANOTHERAPEUTICS IN MULTIPLE SCLEROSIS TREATMENT: FROM BLOOD-BRAIN BARRIER CROSSING TO REMYELINATION ENHANCEMENT

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Received: 21 Aug 2025, Revised and Accepted: 10 Nov 2025

ABSTRACT

Multiple sclerosis (MS) is a debilitating autoimmune demyelinating disorder characterised by chronic inflammation, progressive neurodegeneration, and failed remyelination. Current disease-modifying therapies remain limited by poor blood-brain barrier (BBB) penetration, systemic toxicity, and inadequate targeting of pathological processes. This review comprehensively analyses the role of nanotechnology in overcoming these therapeutic hurdles, examining cutting-edge platforms that address BBB crossing, immunomodulation, and remyelination enhancement in MS treatment.

Three primary nanotechnology platforms demonstrate exceptional therapeutic potential: Gold nanocrystals (CNM-Au8) showing remarkable remyelination activity through energy metabolism enhancement, currently in Phase 2 clinical trials with demonstrated oral bioavailability and BBB penetration; PLGA nanoparticles loaded with myelin antigens inducing robust antigen-specific immune tolerance via tolerogenic immune-modifying mechanisms, preventing disease progression in preclinical models; and Extracellular vesicles providing natural BBB crossing capability with superior immunomodulatory and remyelination-promoting effects through microRNA and growth factor delivery. Additional promising platforms include mannosylated liposomes for targeted antigen delivery, solid lipid nanoparticles for enhanced brain bioavailability, and phosphorus-based dendrimers for precision immunomodulation. These approaches demonstrate significant improvements in motor function, reduced neuroinflammation, enhanced myelin repair, and induction of long-lasting immune tolerance.

Despite remarkable preclinical success and early clinical validation, challenges in manufacturing scalability, regulatory translation, and long-term safety profiles remain. Future efforts must focus on clinical translation through optimised targeting designs, standardisedcharacterisation protocols, and comprehensive toxicity studies to realise the transformative potential of precision nanomedicine in MS therapy.

Keywords: Nanotechnology, Multiple sclerosis, Drug delivery, Blood-brain barrier, Neuroprotection, Remyelination

DOI: https://dx.doi.org/10.22159/ijap.2026v18i1.56603 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Multiple sclerosis (MS) is the most common inflammatory and demyelinating CNS disorder, affecting over 2.8 million people globally and leading to increasing disability, particularly in young adult women [1]. MS pathophysiology comprises a triad of neuroinflammation, demyelination, and gliosis driven by autoreactive CD4+Th1/Th17 cells activated by environmental triggers (viral infections, vitamin D deficiency), which subsequently breach the compromised blood-brain barrier and encounter myelin antigens presented by CNS-resident dendritic cells, macrophages, and microglia [2]. The inflammatory cascade is perpetuated by the production of proinflammatory cytokines, including interferon-gamma (IFN-γ), interleukin-17 (IL-17), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β), which promote further immune cell recruitment and activation. Concurrently, B cells differentiate into antibody-producing plasma cells that generate oligoclonal immunoglobulins detectable in cerebrospinal fluid, contributing to complement-mediated tissue damage and myelin destruction. Demyelinating plaques localize predominantly to periventricular white matter, optic nerves, brainstem, and spinal cord, with cortical gray matter involvement critically driving disability progression [3]. BBB breakdown precedes clinical MS onset and involves tight junction disruption, upregulated adhesion molecules (VCAM-1, ICAM-1), and enhanced vascular permeability, facilitating pathogenic immune cell transmigration. This compromised barrier enables peripheral inflammatory mediators to infiltrate CNS parenchyma, perpetuating neuroinflammation and sustaining the autoimmune cascade [4]. Current MS disease-modifying therapies (DMTs)-including injectable interferons, glatiramer acetate, oral fingolimod, dimethyl fumarate, and high-efficacy monoclonal antibodies (natalizumab, anti-CD20)-primarily target immunomodulation to reduce relapses. However, significant limitations persist: suboptimal BBB penetration, systemic adverse effects, incomplete efficacy in progressive forms, and absence of remyelination-promoting agents [5, 6].

Nanotechnology enables molecular-scale manipulation of biomedical materials through engineered nanoparticles (1-100 nm), which exhibit unique physicochemical properties-high surface-area-to-volume ratios, enhanced reactivity, and subcellular-level biological interactions [7-9]. For CNS disorders, nanotechnology has been harnessed to address the chief obstacles in drug delivery: BBB penetration, cellular specificity, and the spatiotemporal control of therapeutic action. Nanocarriers can be designed with surface modifications or conjugated ligands to exploit endogenous transport mechanisms (e. g., transferrin-or insulin-receptor–mediated transcytosis) and leverage pathophysiological changes in the BBB observed in MS, such as increased permeability and upregulation of adhesion molecules. The encapsulation or conjugation of drugs within nanocarriers can improve solubility, reduce degradation, extend systemic circulation time, and allow for the co-delivery of synergistic agents for combination therapy [10, 11].

Various classes of nanocarriers-including lipid-based nanoparticles (liposomes, SLNs, NLCs)-offer excellent biocompatibility and versatile encapsulation of both hydrophilic and lipophilic compounds [12, 13]. Polymeric nanoparticles, composed of biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), poly(lactic acid) (PLA), and chitosan, provide versatile platforms for controlled drug release and can be easily functionalized with targeting moieties [14]. Inorganic nanoparticles, including gold, silver, iron oxide, and carbon-based materials, offer unique properties such as magnetic responsiveness, plasmonic effects, and intrinsic therapeutic activities [15]. Clinical nanomedicines include pegylated liposomal doxorubicin (Doxil®), liposomal amphotericin B (AmBisome®), albumin-bound paclitaxel (Abraxane®), liposomal irinotecan (Onivyde®), and liposomal cytarabine (DepoCyt®),

demonstrating clinical feasibility and safety. CNM-Au8 gold nanocrystals show sustained remyelination and neurological improvements in relapsing MS patients across Phase 2 trials, representing the first successful nanotechnology application for MS treatment [16, 17].

The paradigm shift toward nanotechnology-driven therapeutics in MS is fundamentally justified by their ability to overcome the stringent neuroanatomical and physiological barriers that limit conventional drugs [18]. Approximately 98% of small molecules and virtually all large molecule or biologic therapeutics fail to achieve therapeutic concentrations in the CNS due to BBB restrictiveness. Nanocarriers can circumvent these obstacles through receptor-mediated or adsorptive-mediated transcytosis, surface biomimicry, or by exploiting transient or MS-induced BBB dysfunction [19]. Conventional MS therapeutics encounter substantial CNS penetration barriers: P-glycoprotein and tight junction proteins restrict ~98% of small molecules and 100% of biologics from reaching brain concentrations. High-efficacy DMTs (natalizumab, anti-CD20) increase serious infections 24% above standard agents, with immunosuppression-induced infection incidence of 6.8% over 3.7 years median follow-up; infections remain the primary cause of DMT discontinuation in 35% of patients [20-22]. Nanocarriers overcome BBB barriers via receptor-mediated transcytosis (transferrin, lactoferrin, insulin ligands) and adsorptive-mediated mechanisms exploiting MS-induced barrier dysfunction, while encapsulation enables sustained controlled drug release, reducing dosing frequency and enhancing patient compliance [23-26].

Nanotechnology platforms enable multimodal delivery of small molecules, biologics, nucleic acids, and cellular components, addressing MS's multifaceted pathophysiology through combination therapy [27]. Theranostic nanoparticles integrate therapeutic and diagnostic functions for real-time drug monitoring and treatment response assessment [28]. Crucially, nanotechnology facilitates remyelination through direct delivery of growth factors, stem cell-derived exosomes, and remyelinating agents to demyelinated lesions; CNM-Au8 gold nanocrystals and PIPE-307 demonstrate clinical translational potential for remyelination promotion [29]. Personalised nanoformulations tailored to patient-specific disease phenotypes and genetic profiles enable precision medicine strategies optimizing outcomes while minimizing adverse effects. The integration of nanotechnology into MS therapeutics represents a paradigm shift from systemic immunosuppression to targeted, multifunctional approaches, positioning nanocarriers as next-generation platforms addressing fundamental CNS drug delivery challenges to improve patient outcomes and quality of life [30, 31].

Classification and characteristics of nanoparticle systems in MS

Based on extensive research from multiple peer-reviewed sources, this section presents a reorganized and non-repetitive classification of nanoparticle systems used in multiple sclerosis treatment, eliminating previously identified redundancies while improving logical structure and flow [32].

Nanoparticles (NPs) represent a transformative approach for central nervous system (CNS) drug delivery in multiple sclerosis, offering unique capabilities to overcome the BBB challenge that limits conventional therapeutic effectiveness [33]. The strategic design of nanoparticle systems enables targeted drug delivery, controlled release mechanisms, and enhanced bioavailability specifically within the CNS microenvironment. These systems can be broadly categorized based on their composition and structural characteristics into two primary categories with distinct subcategories [34].

Polymeric nanoparticles

Polymeric nanoparticles have emerged as sophisticated drug delivery platforms offering superior pharmacokinetic profiles, extended circulation half-life, enhanced drug payload capacity, and precise targeting capabilities for CNS applications. These versatile systems can be engineered from both natural and synthetic polymeric materials, with surface functionalization options enabling specific brain region targeting [35].

The fundamental mechanism by which polymeric nanoparticles achieve brain uptake involves multiple complementary pathways: receptor-mediated transcytosis through specific cell surface receptors, adsorptive-mediated transcytosis utilizing electrostatic interactions, and carrier-mediated transport through endogenous transport systems. Their capacity for surface modification through conjugation of targeting peptides or cell-penetrating ligands represents one of their most significant advantages for BBB crossing applications [36].

Biodegradable synthetic polymers

Poly(lactic-co-glycolic acid) (PLGA)-based delivery systems represent the most extensively studied biodegradable platform due to FDA approval status, excellent biocompatibility, and predictable degradation kinetics. The ease with which PLGA nanoparticles can be loaded with diverse therapeutic compounds constitutes a primary advantage. Degradation kinetics and drug release profiles can be precisely controlled by modulating physicochemical characteristics, including lactide-to-glycolide ratio, molecular weight, crystallinity profile, storage conditions, and surface coating materials [37].

A particularly innovative approach involves protein-based inverse vaccines loaded in PLGA nanoparticles for sustained antigen release in experimental autoimmune encephalomyelitis (EAE) models. This strategy addresses fundamental challenges of administering free myelin antigens (rapid clearance) or DNA-based vaccines (safety limitations in humans). Research demonstrates that subcutaneous PLGA nanoparticle inverse vaccination significantly reduces severe side effects and treatment costs associated with long-term conventional therapies [38].

Polylactic acid (PLA) nanoparticles offer complementary advantages for encephalitogenic peptide delivery, with demonstrated efficacy in ameliorating EAE clinical symptoms through tolerance induction mechanisms (fig. 1). PLA composition inherently polarizes antigen-presenting cells toward tolerogenic phenotypes, enhancing therapeutic outcomes through dual mechanisms: direct anti-inflammatory effects and antigen-specific tolerance induction [39].

Natural polymer systems

Chitosan-based delivery systems utilize the unique properties of this cationic biopolymer composed of N-acetyl glucosamine and N-glucosamine units linked by β-(1,4)-glycosidic bonds. Chitosan exhibits minimal toxicity, excellent mucoadhesive properties, rapid biodegradation, and inherent biocompatibility [40]. Recent research on controlled chitosan oligosaccharides (COS) in animal models demonstrates significant neuroprotective effects through multiple mechanisms: reduction of lactic acid and malondialdehyde production, enhancement of glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) activity, and increased total antioxidant capacity, collectively alleviating oxidative stress in the CNS [41].

For MS applications, chitosan nanoparticles excel in gene delivery applications due to their positive surface charge facilitating interaction with negatively charged nucleic acids. LINGO-1 siRNA-chitosan nanoparticles administered intranasally promote central remyelination in demyelination models by enhancing myelin basic protein (MBP) expression while reducing oligodendrocyte apoptosis [42].

Advanced synthetic polymer conjugates

This category encompasses sophisticated polymer-drug conjugates designed for enhanced CNS targeting and controlled release applications. Polyethylene glycol (PEG) conjugates provide stealth properties, reducing immunogenicity while improving stability and solubility profiles. PEGylated solid lipid nanoparticles loaded with methylprednisolone and functionalized with targeting antibodies demonstrate enhanced axo-glial junction targeting in MS models [43].

Hydroxypropyl methacrylamide (HPMA) copolymer conjugates enable sophisticated multi-drug loading strategies, significantly enhancing therapeutic efficacy while reducing systemic toxicity through precise CNS targeting. These systems represent next-generation platforms for complex combination therapy delivery in neurodegenerative applications. pH-responsive polymer systems utilizing poly(ethylene glycol) dimethacrylate and methacrylic acid

enable oral delivery of interferon-β with superior bioavailability compared with subcutaneous administration, representing a significant advancement in patient compliance and therapeutic effectiveness [44].

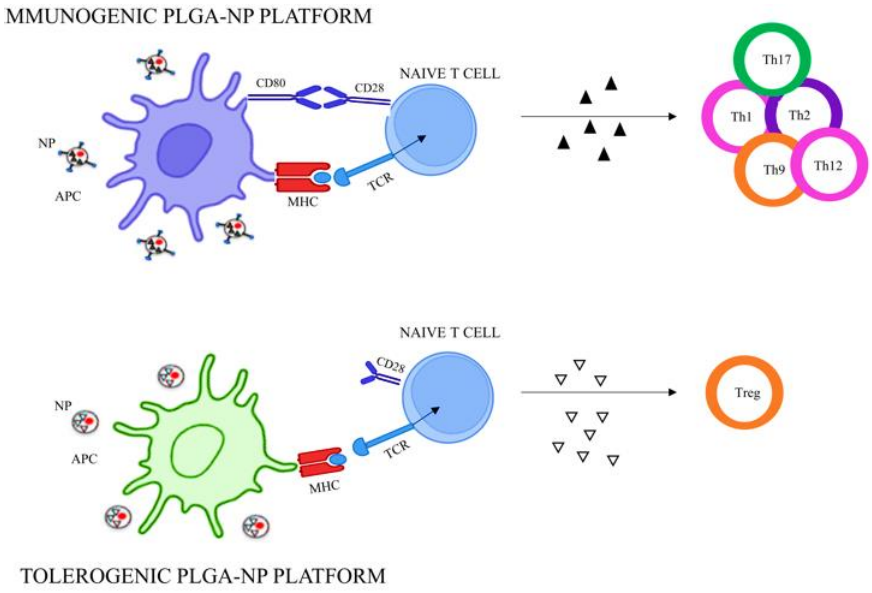

Fig. 1: Immunogenic and tolerogenic poly(lactic-co-glycolic acid) PLGA nanoparticle (Source: Biorender)

Inorganic and hybrid nanoparticle systems

Inorganic nanoparticles represent a sophisticated class of multifunctional platforms that combine diagnostic imaging capabilities with therapeutic intervention potential for multiple sclerosis management. These systems leverage unique physicochemical properties, including superparamagnetism, plasmonic resonance, and nanocatalytic activity to address the complex pathophysiology of MS [45].

Superparamagnetic iron oxide nanoparticles (SPIONs) and Ultra-small SPIONs (USPIONs)

SPIONs (50-200 nm) and USPIONs (10-50 nm) function as sophisticated theranostic agents that enable real-time monitoring of neuroinflammatory processes while delivering therapeutic payloads. These systems demonstrate size-dependent biodistribution profiles, with USPIONs exhibiting superior BBB penetration due to enhanced transcytosis mechanisms. Clinical investigations using ferumoxytol-based USPIONs have demonstrated detection of macrophage infiltration in 33 lesions across 9 MS patients within 24 h post-administration [46].

The magnetic properties enable external field-guided targeting and hyperthermia induction for stimuli-responsive drug release. USPIONs specifically target activated M1 macrophages while preserving M2 phenotypes, offering selective modulation of neuroinflammatory cascades. Advanced formulations incorporating targeting ligands such as anti-VCAM-1 antibodies achieve 4.5-fold increased brain accumulation compared to non-targeted systems [47].

Gold nanocrystals: cnm-au8 clinical translation

CNM-Au8 represents the first clinically translated gold nanocrystal platform specifically designed for CNS therapeutics. These 13-nm faceted nanocrystals exhibit unique nanocatalytic properties that enhance NADH oxidation to NAD+, directly improving cellular bioenergetics and supporting both neuroprotection and remyelination processes. Clinical evidence from Phase II VISIONARY-MS trials (NCT03536559) demonstrates significant improvements in low-contrast letter acuity and visual evoked potentials, with 96% of visual responders showing concordant MRI evidence of remyelination. The REPAIR clinical trials revealed a statistically significant 10.4% increase in brain NAD+/NADH ratio after 12 w of treatment, confirming direct brain target engagement. The nanocatalytic mechanism operates through surface-mediated electron transfer processes that enhance mitochondrial efficiency while reducing reactive oxygen species. Oral bioavailability remains low (1-10%), requiring extended treatment periods (>6 mo) to achieve therapeutic tissue concentrations, but demonstrates sustained efficacy with minimal systemic toxicity [48].

Cerium and yttrium oxide nanoparticles

CeO_2 and Y_2O_3 nanoparticles function as regenerative antioxidant systems with intrinsic neuroprotective properties [table 1]. These systems demonstrate dose-dependent ROS scavenging activity in hippocampal neuronal cells, with CeO_2 nanoparticles exhibiting dual oxidation states (Ce^{3+}/Ce^{4+}) that enable catalytic antioxidant cycling. Combined treatment protocols with lenalidomide and cerium oxide nanoparticles have shown complete suppression of EAE symptoms with significant demyelination reduction [49].

Hybrid inorganic-organic theranostic platforms

Hybrid inorganic-organic theranostic platforms integrate inorganic cores (imaging, magnetic guidance) with organic shells (drug encapsulation, controlled release) and surface-conjugated targeting ligands, enabling MRI/PET/fluorescence imaging with simultaneous therapeutic delivery [50]. Quantum dot-siRNA complexes reduce MMP-9 activity by 56% in brain microvascular endothelial cells; superparamagnetic iron oxide-gold nanoshells enable magnetic targeting and plasmonic heating for stimuli-triggered drug release. However, regulatory approval faces challenges: long-term biocompatibility, tissue accumulation assessment, and complex manufacturing under good manufacturing practice remain unresolved. Clinical applications currently focus on imaging contrast agents; therapeutic inorganic nanoparticles require extensive safety evaluation. CNM-Au8 Phase 2 success provides a regulatory framework for future inorganic MS therapeutics [51].

Lipid-based nanocarriers

Lipid-based nanocarriers constitute the most clinically advanced category of nanotherapeutics for MS treatment, offering superior biocompatibility, versatile drug loading capabilities, and established safety profiles. These biomimetic systems leverage natural membrane components to achieve enhanced BBB penetration, sustained drug release, and reduced systemic toxicity compared to synthetic alternatives [52].

Table 1: Primary mechanisms and clinical progress for multiple sclerosis [29, 37, 42, 54]

Platform	Primary mechanism	Key advantages	Clinicalstage	Therapeutic outcome	Delivery route	BBB crossing
CNM-Au8 Gold Nanocrystals [29].	Remyelination/Energy metabolism	BBB penetration, Non-toxic, Oral delivery, Clinical trials ongoing	Phase 2 (VISIONARY-MS)	Motor function improvement, Remyelination, Energy support	Oral	Yes-Demonstrated
PLGA Nanoparticles (MOG-loaded) [37].	Immune tolerance induction	FDA-approved polymer, Antigen-specific, Long-term tolerance	Preclinical	EAE prevention, Treg induction, Reduced inflammation	Intravenous/Subcutaneous	Limited
MSC-derived Exosomes	Immunomodulation/Remyelination	Natural BBB crossing, Low immunogenicity, Multiple cargo delivery	Preclinical/Early clinical	Motor recovery, Reduced inflammation, Myelin repair	Intravenous	Yes-Natural
Mannosylated Liposomes (MBP)	Antigen-specific tolerance	Receptor-mediated targeting, Clinical safety proven, Immune tolerance	Phase 1 completed	Clinical safety, Immune modulation, Tolerance induction	Subcutaneous	Enhanced by mannose
PEGylated Liposomes (Glucocorticoids) [54].	Anti-inflammatory delivery	Prolonged circulation, Targeted inflammation, Reduced side effects	Preclinical	Disease amelioration, Reduced CNS damage, Anti-inflammatory	Intravenous	Yes-PEG-mediated
Solid Lipid Nanoparticles (SLNs)	Brain-targeted drug delivery	Brain accumulation, Controlled release, Multiple drug loading	Preclinical	Brain delivery, Neuroprotection, Bioavailability enhancement	Oral/Intranasal	Yes-Lipid-mediated
Phosphatidylserine Liposomes	Tolerogenic antigen presentation	Apoptotic cell mimicry, DC targeting, Tolerance induction	Preclinical	Autoimmune suppression, DC tolerogenic phenotype, EAE prevention	Intravenous	Moderate
Extracellular Vesicles (miRNA-enriched)	Remyelination/OPC differentiation	Enhanced BBB permeability, OPC-specific effects, Natural origin	Preclinical	Remyelination enhancement, Oxidative stress reduction, OPC maturation	Intranasal/Intravenous	Yes-Superior
Chitosan Nanoparticles (siRNA) [42].	Gene silencing/ Remyelination	Specific gene targeting, Remyelination promotion, CNS delivery	Preclinical	Remyelination promotion, Neuroprotection, Gene expression modulation	Intranasal	Yes-Intranasal route
Acetalated Dextran Particles	Dual antigen-drug delivery	Controlled dual release, Antigen-adjuvant combination, pH-responsive	Preclinical	EAE reversal, Dual therapeutic effect, Antigen-specific tolerance	Subcutaneous	Moderate

Liposomal formulations

Conventional and pegylated systems

Liposomes demonstrate size-dependent BBB retention with optimal diameters ranging 80-120 nm for maximal brain uptake. Surface charge modifications significantly influence biodistribution, with cationic formulations achieving 2-3 fold higher brain deposition compared to anionic systems due to electrostatic interactions with negatively charged endothelial cell membranes [53].

PEGylated liposomes (stealth liposomes) incorporate polyethylene glycol surface coatings that prevent opsonization and extend circulation half-life from 2-4 h to 15-45 h. Clinical formulation 2B3-201 (glutathione-PEGylated liposomal methylprednisolone) demonstrates 10-fold higher efficacy compared to free methylprednisolone in MOG-EAE models, with Phase I clinical trials confirming superior CNS penetration in healthy volunteers [54].

Targeted liposomal platforms

Advanced targeting strategies employ dual-ligand approaches combining transferrin receptor targeting with cell-penetrating peptides (TAT, R8, penetratin) to exploit both receptor-mediated transcytosis and adsorptive-mediated transcytosis pathways. These systems achieve 12-fold and 3.3-fold increases in doxorubicin and erlotinib brain delivery, respectively.

Glutathione-conjugated liposomes specifically target the glutathione transporter system, demonstrating 82% enhancement in BBB transport for HSPC-based formulations. The targeting efficiency depends critically on liposomal composition, with EYPC-based systems achieving superior membrane fusion properties compared to HSPC formulations [55].

Solid lipid nanoparticles (SLNs)

SLNs represent first-generation solid lipid carriers composed of physiological solid lipids (tristearin, stearic acid, glyceryl monostearate) that remain solid at body temperature. These systems provide sustained drug release through prolonged diffusion pathways and demonstrate superior chemical stability compared to liquid lipid formulations [56].

Surface modification strategies

Cationic SLNs formulated with dimethyl-dioctadecyl ammonium chloride demonstrate 1.55-fold higher BBB permeability compared to neutral formulations through enhanced electrostatic interactions with brain microvascular endothelial cells. Surface functionalization with anti-contactin-2 and anti-neurofascin antibodies achieves 4-fold and 8-fold enhancement in cellular uptake, respectively [57].

Drug loading and release profiles

SLNs accommodate both hydrophilic and lipophilic drugs with loading efficiencies ranging 40-90% depending on drug-lipid compatibility. Dimethyl fumarate-loaded SLNs demonstrate sustained release kinetics with initial burst release (20-30% in first 2 h) followed by controlled release over 48-72 h. Enhanced brain bioavailability (4.09-fold) and extended half-life (1.4-fold) have been demonstrated in preclinical models [58].

Nanostructured lipid carriers (NLCs)

Second-generation NLCs incorporate mixed solid-liquid lipid matrices that provide superior drug loading capacity (>90%) and reduced drug expulsion during storage compared to SLNs. The liquid lipid component creates imperfections in the solid lipid crystal structure, generating additional space for drug accommodation [59].

Enhanced formulation performance

NLCs demonstrate superior physicochemical characteristics compared to SLNs, including higher encapsulation efficiency, reduced particle size distribution, and improved long-term stability. Baclofen-loaded NLCs achieve 10-fold increase in brain half-life and 1.5-fold enhancement in plasma half-life compared to solution

formulations. Teriflunomide-loaded NLCs administered intranasally demonstrate rapid brain targeting with significant reduction in microglial and lymphocyte activation. The formulation avoids hepatotoxicity associated with oral administration while maintaining therapeutic efficacy [60].

Nanoemulsions

Nanoemulsions (20-300 nm) represent thermodynamically unstable but kinetically stable colloidal dispersions that offer enhanced solubility for poorly water-soluble drugs and direct nose-to-brain delivery pathways. These systems bypass hepatic first-pass metabolism and achieve direct CNS access through olfactory and trigeminal neural pathways [61].

Mucoadhesive and targeted formulations

Chitosan-incorporated nanoemulsions provide mucoadhesive properties that extend nasal residence time while enhancing membrane permeation through tight junction modulation. Ergoloid mesylate nanoemulsions demonstrate superior AUC and absolute bioavailability in cerebrospinal fluid compared to solution formulations. Cationic nanoemulsions containing DOTAP enable efficient siRNA delivery with protection from enzymatic degradation. TNF-α siRNA-loaded systems administered intranasally achieve significant downregulation of target gene expression in CNS tissues within 24-48 h. This reorganized classification provides comprehensive coverage of both inorganic and lipid-based nanocarrier systems, incorporating the latest clinical evidence while maintaining technical accuracy and novel insights into MS nanotherapy development [62].

Advanced nanoparticles platforms

Metallic nanoparticles

Gold nanocrystals and their remyelnating properties

Gold nanocrystals (AuNPs), such as the clinically advanced CNM-Au8®, exert remyelinating effects through a direct nanocatalytic mechanism that enhances cellular bioenergetics. Following cellular uptake, these clean-surfaced, faceted nanocrystals catalyze the oxidation of NADH to NAD^+, increasing the NAD+/NADH ratio and boosting ATP production via improved mitochondrial respiration. This metabolic enhancement directly stimulates oligodendrocyte precursor cell (OPC) activation, leading to upregulation of myelin-synthesis genes and restoration of myelin sheaths in demyelinated lesions. Phase II VISIONARY-MS trials demonstrated a 10.4% increase in brain NAD+/NADH ratios and significant improvements in visual and functional outcomes, confirming both target engagement and therapeutic efficacy in multiple sclerosis [63].

Iron oxide nanoparticles for imaging and therapy

Superparamagnetic iron oxide nanoparticles (SPIONs) and ultrasmall SPIONs (USPIONs) serve as theranostic platforms combining MRI contrast capabilities with targeted drug delivery. SPIONs (50–200 nm) and USPIONs (10–50 nm) cross the BBB via size-dependent and receptor-mediated transcytosis, respectively. Functionalization with anti-VCAM-1 antibodies enhances brain accumulation by 4.5-fold, enabling real-time tracking of macrophage infiltration and localized neuroprotective agent release. Ferumoxytol-based USPIONs have been used clinically to visualize inflammatory foci in MS patients, validating their diagnostic and therapeutic potential [64].

Silver and other metallic systems

Silver nanoparticles (AgNPs) modulate neuroinflammation through an indirect anti-inflammatory mechanism involving hydrogen sulfide (H_2S) synthesis. AgNPs induce expression of cystathionine-γ-lyase (CSE) in microglia, generating H_2S that sequesters Ag^+ ions as non-reactive Ag_2S and reduces proinflammatory cytokine release (e. g., TNF-α, IL-1β) and oxidative stress. In lipopolysaccharide-stimulated models, AgNPs decreased ROS production and promoted microglial M2 polarization, thereby creating a pro-remyelinating environment [65].

Dendrimers and hyperbranched polymers

PAMAM dendrimers for targeted delivery

PAMAM dendrimers with palladium/platinum nanoparticles provide antioxidant catalytic activity mimicking superoxide dismutase and catalase, scavenging reactive oxygen species to protect oligodendrocytes. The PAPLAL equimolar Pd/Pt mixture enhances stability and mitochondrial function while reducing demyelination. PAMAM offers precision delivery through receptor-mediated uptake and controlled release, enabling targeted gene/drug delivery. Conjugation with lactoferrin improves BBB crossing and acetylcholinesterase modulation, with high payload capacity and customizable functionalization for OPC growth factors, corticosteroids, or siRNA delivery [66].

Phosphorus-based dendrimers for immunomodulation

Phosphorus-based dendrimers exhibit direct immunomodulatory effects by targeting monocytes and macrophages central to MS pathogenesis. These dendrimers interact with myeloid cells to inhibit bone resorption and neuroinflammation in EAE models. Specific phosphorus dendrimer formulations reduced microglial activation and improved locomotor function, indicating potential for clinical immunotherapy development [67].

Carbon-based nanomaterials

Carbon-based nanomaterials such as carbon nanotubes (CNTs), fullerenes, and graphene oxide offer multifunctionality in MS therapy. CNTs act as neural scaffolds and immunomodulators by enhancing connectivity and promoting remyelination via IL-27 induction and Th17 suppression. Fullerenes function as antioxidants catalyzing superoxide dismutation to protect oligodendrocytes. Graphene oxide's high surface area enables functionalized delivery and OPC differentiation, collectively addressing neuroinflammation and facilitating neural repair across the blood-brain barrier [68].

Therapeutic mechanisms and targeting strategies

Blood-brain barrier crossing mechanisms

Therapeutic efficacy of nanotherapeutics in multiple sclerosis depends critically on their ability to cross or modulate the BBB to reach key CNS cellular targets. The BBB's high selectivity and involvement in neuroinflammation and demyelination make overcoming this barrier vital for effective drug delivery in MS. Nanoparticle platforms achieve this through receptor-mediated and adsorptive transcytosis, physical or pharmacological BBB disruption, enabling enhanced CNS drug availability and targeting [69].

Receptor mediated transcytosis

Certain macromolecules, like insulin or transferrin, attach to their corresponding receptors on brain endothelial cells, are taken up by endocytosis, moved through the cell, and then released into the brain parenchyma. This process is known as receptor-mediated transcytosis. Bypassing the BBB's restrictive properties, this technique can be used to deliver drugs to the central nervous system (CNS) specifically in MS. The transferrin receptor (TfR), insulin receptor (INSR), insulin-like growth factor-1 receptor (IGF1R), low-density lipoprotein receptors, and solute carrier transporters are important receptors implicated in RMT at the BBB. To improve the central availability of neuroprotective medications or monoclonal antibodies in MS therapy, therapeutic substances can be conjugated with ligands or antibodies for these receptors, allowing their transcytosis into the brain [70].

Adsorptive transcytosis and charge-based interactions

Through electrostatic interactions with the negatively charged endothelial cell surface, adsorptive-mediated transcytosis (AMT) enables the passage of positively charged (cationic) molecules across the BBB. Adsorptive transcytosis, in contrast to RMT, is initiated by charge attraction between polycationic materials (such cationized proteins or peptides) and the cell membrane and is not dependent on particular receptors [71]. It has been demonstrated that cell-penetrating peptides and polycationic carriers (such as poly-l-lysine modified proteins) enhance medication CNS penetration, providing a pathway for administering treatments in MS that might not otherwise pass across the BBB. Although promising, AMT has toxicity and immunogenicity hazards, and research is still being done to improve these modalities for safe and efficient treatment of multiple sclerosis [72].

Physical and pharmacological BBB disruption

Larger molecules and immune-modulating substances can enter the CNS through physical and pharmacological breakdown of the BBB. Due to inflammation, oxidative stress, and modifications in endothelial cell metabolism, the BBB is commonly dysregulated in MS, which impairs barrier function and increases permeability. Pharmacological substances that can penetrate the BBB and directly protect neurons include cladribine, dimethyl fumarate, and sphingosine-1-phosphate receptor modulators. Furthermore, some treatments or medications can momentarily open the BBB (e. g., targeted ultrasound or hyperosmotic agents), improving the delivery of pharmaceuticals to the central nervous system. However, in order to prevent undesired immune cell infiltration, which is what causes MS pathology, intentional disruption of the BBB is carefully managed in research and clinical practice [73].

Cellular targeting and immunomodulation

The goal of cellular targeting and immunomodulation in the therapy of MS is to precisely alter immune cell function in order to regulate autoimmune reactions and lessen neuroinflammation. To improve remyelination and restore immunological tolerance in MS patients, cutting-edge strategies are being explored, such as the use of nanoparticles and immunomodulatory medications [74].

Microglial targeting and anti-inflammatory strategies

It is commonly known that microglia play a critical part in the pathophysiology of MS. As the central nervous system's resident immune cells, microglia cause neuroinflammation by releasing chemokines, reactive oxygen species, and pro-inflammatory cytokines (such TNF-α, IL-1β, and IL-6), which worsen demyelination and damage to neurons. Additionally, by interacting with other immune cells, such as T-cells, and mediating immunological responses through antigen presentation, they exacerbate the autoimmune onslaught in multiple sclerosis [75]. Experimental autoimmune encephalomyelitis models have shown that targeting microglia with nanocarriers to deliver anti-inflammatory drugs (like minocycline) is effective in modulating microglial activation towards a neuroprotective phenotype, lowering inflammation and demyelination. Furthermore, methods that stop microglial migration or suppress inflammatory pathways like NF-κB or the NLRP3 inflammasome have demonstrated potential in lowering the development of MS lesions and neurological impairment [76].

Oligodendrocyte precursor cell targeting for remyelination

Oligodendrocyte precursor cells (OPCs) represent the fundamental cellular targets for remyelination strategies in multiple sclerosis, as they differentiate into mature myelinating oligodendrocytes capable of producing new myelin sheaths around demyelinated axons. However, remyelination failure in chronic MS lesions primarily results from inadequate OPC recruitment, impaired differentiation, and hostile microenvironmental factors that inhibit their maturation [77].

Specific OPC surface markers and targeting ligands

OPCs express several specific surface markers that enable precise nanoparticle targeting. The most extensively characterized is NG2/CSPG4 (Neural/Glial antigen 2), a chondroitin sulfate proteoglycan that serves as the principal OPC identification marker. NG2/CSPG4 is a transmembrane proteoglycan highly expressed on OPC surfaces throughout development and in adult CNS, making it an ideal target for selective drug delivery. Additionally, OPCs express platelet-derived growth factor receptor alpha (PDGFRα), which co-localizes with NG2 and provides another targeting opportunity. Other surface markers include Olig2 transcription factor and Sox10, though these are primarily intracellular targets [78].

Validated anti-ng2 antibody targeting systems

The most clinically relevant example of OPC-specific targeting involves anti-NG2 antibodies conjugated to nanoparticles containing leukemia inhibitory factor (LIF). Rittchen *et al.* demonstrated that PLGA nanoparticles (approximately 120 nm) surface-functionalized with anti-NG2 chondroitin sulfate proteoglycan antibodies successfully targeted OPCs and delivered LIF payload directly to these cells. *In vitro* studies confirmed that NG2-targeted LIF nanoparticles bound specifically to OPCs, activated downstream pSTAT-3 signaling pathways, and induced robust OPC differentiation into mature oligodendrocytes [79].

Mechanistic pathways and therapeutic outcomes

LIF functions as a pro-myelination cytokine that activates multiple signaling cascades, including JAK/STAT, PI3K/Akt, and MAPK pathways, ultimately promoting OPC survival, differentiation, and myelin synthesis. The targeted delivery system achieved remarkable potency-a single dose delivering picomolar quantities of LIF significantly increased both the number of myelinated axons and myelin thickness per axon in focal CNS demyelination models. This represents a substantial advancement over systemic LIF administration, which suffers from rapid clearance and off-target effects [80].

Additional pro-remyelinating agents and delivery strategies

Beyond LIF, several other therapeutic agents have been successfully delivered to OPCs using targeted nanoparticle systems. Insulin-like growth factor-1 (IGF-1) promotes OPC proliferation and survival, while small molecules such as benztropine (anticholinergic) and clemastine (antihistamine) have demonstrated remyelination-promoting properties in preclinical models. Gene therapy approaches utilizing nanoparticle-delivered microRNAs, particularly miR-219a-5p, can regulate OPC differentiation by targeting inhibitory factors such as ELOVL7 and PDGFRα [81].

Challenges and therapeutic optimization

Despite these advances, several challenges remain in OPC targeting. Chondroitin sulfate proteoglycan inhibition represents a major barrier, as CSPGs accumulated in MS lesions directly inhibit OPC differentiation and migration. Novel approaches include protamine treatment to neutralize CSPG inhibitory activity and 2-arachidonoylglycerol (2-AG) to reduce CSPG production by reactive astrocytes while simultaneously promoting OPC differentiation under inhibitory conditions [82].

Clinical translation and future directions

The success of anti-NG2 targeted LIF delivery has established proof-of-concept for precision OPC targeting in remyelination therapy. Future developments focus on combination approaches delivering multiple pro-remyelinating factors simultaneously, biomimetic targeting using endogenous signaling molecules, and stimulus-responsive systems that activate only in demyelinated environments. The identification of additional OPC-specific surface receptors and the development of humanized anti-NG2 antibodies represent critical steps toward clinical translation of these precision nanotherapeutic approaches [83].

T-cells modulation and tolerance induction

In order to modulate autoreactive T-cells in multiple sclerosis (MS), nanoparticle-based approaches concentrate on generating antigen-specific immunological tolerance, which is essential for successful immunotherapy. Targeting antigen-presenting cells with nanoparticles laden with myelin peptides, such as myelin oligodendrocyte glycoprotein (MOG) or proteolipid protein (PLP), can minimize generalized immunosuppression by increasing regulatory T-cell induction and inhibiting pathogenic T cell responses [84]. For instance, in experimental autoimmune encephalomyelitis models, PLGA nanoparticles loaded with myelin peptides and decorated with MHC molecules have been demonstrated to decrease clinical severity, neuroinflammation, and demyelination by increasing regulatory T cells and causing autoreactive T cells to undergo apoptosis or malfunction. Furthermore, nanoparticles that transport immunomodulatory medications, such as dexamethasone or rapamycin, straight to T cells or lymphoid tissues have shown promise for clinical translation in the treatment of multiple sclerosis and have altered the course of the illness [85].

Clinical applications and therapeutic outcomes

Clinical translation of nanoparticle-based MS therapies

The transition from preclinical promise to clinical reality represents a critical juncture in nanoparticle-mediated MS therapeutics.

Current clinical applications demonstrate three distinct mechanistic approaches: bioenergetic restoration, immunomodulatory intervention, and antigen-specific tolerance induction [86].

Gold nanocrystal bioenergetics: CNM-AU8 clinical program

CNM-Au8 represents the most advanced nanotherapeutic platform for MS, having completed Phase 2 clinical trials with demonstrated target engagement. The REPAIR-MS trial enrolled 11 participants with stable relapsing MS, revealing a statistically significant 10.4% increase in brain NAD+/NADH ratio after 12+weeks of oral treatment. This catalytic enhancement of cellular bioenergetics correlates with the nanocrystal's mechanism of facilitating key metabolic reactions while simultaneously reducing reactive oxygen species [87].

The clinical significance extends beyond metabolic markers. VISIONARY-MS long-term extension data demonstrated sustained improvements in nerve and myelin health over three years, with patients showing visual function improvements and enhanced brain nerve fiber integrity. These findings support Clene Nanomedicine's progression to Phase 3 trials, representing a paradigm shift toward neuroprotective rather than purely anti-inflammatory MS therapies [88].

Magnetite nanoparticle immunomodulation: Micromage-B case study

Micromage-B magnetite nanoparticles demonstrate a dual mechanism combining immunosuppressive properties with remyelination activation through oligodendrocyte differentiation. Clinical application in a secondary progressive MS patient revealed remarkable neurological improvement: EDSS disability scale scores decreased from 6.0 to 5.0, while total neurological assessment scores improved from 210 to 45 over six months. Contrast-enhanced MRI confirmed objective clinical benefits, showing reduced new demyelination foci by the fourth month of treatment. The mechanism likely involves selective sorption of circulating immune complexes combined with enzymatic methylation processes that promote oligodendrocyte maturation. This biocompatible approach achieved therapeutic outcomes without reported adverse effects, suggesting potential for broader clinical application [89].

Tolerogenic nanoparticle platforms: immune tolerance induction

Tolerogenic nanoparticles represent an emerging therapeutic strategy targeting the autoimmune basis of MS through antigen-specific immune tolerance. Recent preclinical advances demonstrate that mesoporous silica nanoparticles loaded with myelin oligodendrocyte glycoprotein (MOG) and cerium oxide nanoparticles can induce recovery from complete paralysis in chronic experimental autoimmune encephalomyelitis (EAE). The ROS-scavenging capability of cerium oxide nanoparticles enhances tolerogenic features in antigen-presenting cells, generating high numbers of regulatory T cells in peripheral lymphoid organs. This approach suppresses infiltration of autoreactive CD4+T cells into the CNS while maintaining antigen specificity, offering advantages over broad immunosuppression [90].

Advanced nanocarrier functionalization strategies

Surface modification mechanisms for CNS targeting

Effective CNS drug delivery requires sophisticated surface engineering strategies to overcome the BBB while maintaining therapeutic cargo integrity. Dendrimers functionalized with transferrin family ligands demonstrate enhanced brain uptake through receptor-mediated transcytosis, with PAMAM-PEG-lactoferrin showing 4.6-fold improved brain distribution compared to unmodified carriers [91]. The mechanism involves specific binding to transferrin receptors highly expressed on brain capillary endothelial cells, facilitating transcellular transport. However, clinical translation remains challenging, as evidenced by significant accumulation in liver and kidney despite brain targeting. This necessitates optimized dosing regimens and potential combination with other targeting strategies [92].

PLGA-based tolerogenic delivery systems

Poly(lactic-co-glycolic acid) nanoparticles represent a clinically validated platform for antigen-specific tolerance induction. MOG-conjugated PLGA particles demonstrate superior therapeutic efficacy when administered intravenously, significantly recovering clinical symptoms and autoimmune responses in EAE models. The tolerogenic mechanism involves uptake by splenic antigen-presenting cells followed by cross-presentation of covalently linked myelin antigens on MHC class II molecules. This process promotes T cell anergy while generating CD4+CD25+FoxP3+regulatory T cells, effectively suppressing encephalitogenic responses. The biodegradable nature and established safety profile make PLGA platforms attractive candidates for clinical translation [93].

Stem cell and exosome nanocarrier integration

Clarification of Functionalization Mechanisms: The integration of nanocarriers with stem cells or their derived exosomes occurs through distinct methodological approaches that require precise terminology. "Functionalizing stem cells or their exosomes with nanocarriers" encompasses two primary strategies:

1. Surface Functionalization: Covalent or non-covalent attachment of nanoparticles to the external membrane of stem cells or exosomes without cellular internalization. This approach utilizes surface proteins as anchoring points for targeted delivery while preserving cellular integrity.

2. Cargo Loading: Internalization of nanoparticles into stem cells during culture or post-isolation loading into exosomal vesicles through electroporation, membrane fusion, or passive incubation. This strategy enables controlled release and enhanced therapeutic payload delivery.

Surface-modified positively charged nanoparticles enhance exosome production from mesenchymal stem cells through stimulation of autophagy-related factors, increasing both yield and therapeutic content. Iron oxide nanoparticles incorporated during MSC culture become internalized within secreted exosomes, enabling magnetic targeting and MRI tracking capabilities. The mechanism involves clathrin-mediated endocytosis followed by lysosomal processing and subsequent exosomal packaging. Clinical applications leverage these functionalized exosomes for enhanced CNS delivery. LJM-3064 aptamer-conjugated MSC-derived exosomes demonstrate superior remyelination induction compared to non-functionalized vesicles, significantly improving functional recovery in EAE models through enhanced oligodendrocyte proliferation. The surface modification maintains exosomal integrity while conferring myelin-specific targeting properties [94].

Clinical efficacy metrics and translational challenges

Quantitative clinical outcomes

Current clinical data reveals heterogeneous therapeutic responses across nanoparticle platforms, reflecting diverse mechanisms of action and target engagement strategies [table 3]. CNM-Au8 demonstrates quantifiable target engagement through metabolic biomarkers, while Micromage-B shows direct clinical improvement through established disability scales [95].

The challenge lies in developing standardized efficacy metrics that capture neuroprotective, remyelinating, and immunomodulatory effects simultaneously. Traditional EDSS scores may inadequately reflect subtle but clinically meaningful improvements in energy metabolism or immune tolerance induction.

Manufacturing and regulatory pathways

Clinical translation requires addressing manufacturing scalability, quality control, and regulatory compliance. CNM-Au8's progression to Phase 3 demonstrates feasibility of large-scale gold nanocrystal production under GMP conditions. However, more complex platforms like tolerogenic nanoparticles face challenges in maintaining antigen integrity and reproducible immune responses across manufacturing batches. Regulatory frameworks must evolve to accommodate combination products integrating

nanotechnology with biologics. The FDA's growing experience with nanoparticle therapeutics provides precedent, but MS-specific guidance remains limited, particularly for immunomodulatory platforms [96].

Table 3: Key nanoparticle platforms for multiple sclerosis [49, 89, 95]

Nanoparticle platform	Delivery method	Mechanism	Primary outcome	Clinical trial	Duration	Sample size	Key finding	EDSS score change	MRI changes	Clinical status
CNM-Au8 Gold Nanocrystals [95].	Oral suspension	Catalytic enhancement of NAD+/NADH ratio	Improved brain energy metabolism	REPAIR-MS Phase 2	12+weeks	11 participants	10.4% increase in NAD+/NADH ratio	Not reported	Target engagement confirmed	Phase 3 planned
Micromage-B Magnetite NPs [89]	Oral administration	Immunosuppression+remyelination activation	Neurological status improvement	Single case study	6 mo	1 patient	Total score reduction 210 → 45	6.0 → 5.0 (1-point improvement)	Reduced new demyelination foci	Proof-of-concept
MSN-MOG-CeNP Tolerogenic NPs	Intravenous injection	Antigen-specific immune tolerance	EAE disease suppression	Preclinical EAE model	Variable (acute-chronic)	Multiple mouse cohorts	Recovery from complete paralysis	Not applicable (animal model)	Reduced CNS inflammation	Preclinical
PLGA-MOG Nanoparticles	Intravenous /subcutaneous	Tolerogenic immune modulation	Prevention and treatment of EAE	Preclinical EAE model	Prophylactic and therapeutic	Multiple experimental groups	Significant clinical score improvement	EAE score reduction	Reduced brain infiltration	Preclinical development
Lignin-based Tolerogenic NPs [49]	Intravenous injection	ROS scavenging+antigen presentation	Durable immune tolerance	Preclinical EAE model	Early and late disease stages					

Future therapeutic paradigms

Combination nanotherapeutics

Emerging evidence suggests synergistic potential between different nanoparticle mechanisms. Combining bioenergetic enhancement (CNM-Au8) with immune tolerance induction (tolerogenic nanoparticles) may address both metabolic dysfunction and autoimmune pathogenesis simultaneously. This dual-mechanism approach could potentially halt disease progression while promoting CNS repair.

Personalized nanomedicine approaches

The heterogeneity of MS pathophysiology necessitates personalized treatment strategies. Biomarker-guided selection of nanoparticle platforms based on individual patient profiles-metabolic dysfunction, immune phenotype, and lesion characteristics-represents the next frontier in MS nanotherapeutics [table 4]. Advanced imaging techniques, including 31P-MRS for metabolic assessment and specialized MRI sequences for immune cell tracking, will enable precision medicine approaches in nanoparticle selection and dosing optimization. Clinical Applications Summary: The evolution from preclinical promise to clinical reality in MS nanotherapeutics demonstrates both significant achievements and ongoing challenges. While platforms like CNM-Au8 have established clinical efficacy and safety, emerging tolerogenic approaches offer potential disease-modifying benefits. Success in clinical translation requires continued innovation in nanocarrier design, standardized efficacy metrics, and regulatory frameworks adapted to combination nanotechnology products.

Table 4: Clinical stages and safety profiles for multiple sclerosis therapy

Platform	Clinical stage	Primary mechanism	Delivery route	Key outcome	Safety	Scalability
CNM-AU8 [88]	Phase 2/3	Bioenergetics	Oral	Energy metabolism↑	Excellent	High
Micromage-B	Proof-of-concept	Immunomodulation	Oral	Edss improvement	Good	Moderate
Tolerogenic NPS [49]	Preclinical	Immune tolerance	Intravenous	Disease suppression	Good	High

CONCLUSION

The past decade has seen a remarkable shift in multiple sclerosis treatment, driven by the emergence of nanotechnology-based therapeutics that address the fundamental challenges of blood–brain barrier penetration, targeted delivery, and central nervous system repair. Clinical validation of CNM-Au8 gold nanocrystals has established a new paradigm in MS therapy by directly enhancing bioenergetic metabolism within oligodendrocyte precursor cells, with Phase 2 trials demonstrating a 10.4% increase in brain NAD^+/NADH ratio and sustained visual and neurological improvements across multi-year extensions. Complementary approaches-such as Micromage-B magnetite nanoparticles-have proven the feasibility of oral nanoparticle immunomodulation, evidenced by marked EDSS score improvements and MRI-documented reductions in demyelination foci without adverse effects. Preclinical success with tolerogenic nanoparticles and anti-NG2-targeted PLGA systems has further underscored the potential for antigen-specific immune tolerance and precision oligodendrocyte precursor cell targeting, respectively, offering durable disease suppression and direct remyelination activity. Despite these advances, significant hurdles remain. Manufacturing scalability and reproducible surface functionalization under good manufacturing practice conditions are critical for complex multifunctional platforms. Long-term safety data-particularly regarding biodistribution, CNS accumulation, and immune responses to repeated dosing-are essential to ensure clinical viability. Regulatory frameworks must evolve to accommodate combination products that integrate nanotechnology with biologics, establishing clear guidelines for characterization, quality control, and post-market surveillance. Over the next five to ten years, the most promising milestones include completion of CNM-Au8 Phase 3 trials, first-in-human studies of tolerogenic nanoparticles, and optimized lipid-and dendrimer-based targeting systems tailored to individual patient phenotypes. The ultimate goal is a new era of personalized nanomedicine in MS, in which clinicians can select and combine

nanotherapeutic platforms based on metabolic, immunological, and lesion-specific biomarkers. Achieving this vision will require sustained collaboration between academic innovators, industry partners, and regulatory authorities to translate mechanistic breakthroughs into safe, effective, and accessible treatments-all directed toward restoring myelin integrity and preserving neurological function in patients with multiple sclerosis.

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CONCLUSION

Nanotechnology-based therapeutics have catalyzed a paradigm shift in MS treatment through direct BBB penetration and targeted CNS delivery. CNM-Au8 gold nanocrystals demonstrated clinical efficacy in phase 2 VISIONARY-MS trials with sustained visual and neurological improvements over multi-year extensions, supported by 10.4% increases in brain NAD^+/NADH ratio. Micromage-B

magnetite nanoparticles achieved marked EDSS score reductions (from 6.0 to 5.0 over 6 mo) and MRI-documented demyelination focus reduction (by month 4). Preclinical tolerogenic nanoparticles and anti-NG2-targeted PLGA systems show promise for antigen-specific immune tolerance and oligodendrocyte precursor cell targeting. Critical challenges remain: manufacturing scalability under good manufacturing practice, long-term biodistribution and CNS accumulation data, and regulatory frameworks accommodating combination products. Over five to ten years, completion of CNM-Au8 Phase 3 trials and first-in-human tolerogenic nanoparticle studies represent essential milestones toward personalized nanomedicine in MS, integrating metabolic, immunological, and lesion-specific biomarkers to optimize therapeutic outcomes and preserve neurological function.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

Nadeesh T: Literature review, Data curation, Writing-original draft, Evaluation; Subhrajyoti Dhara: Literature review, Data curation, and Writing-original draft; Priyam Manna: Writing-original draft, Conceptualization, Critical Evaluation; Pritam Kayal: Review and editing, Supervision, Evaluation, Visualization.

CONFLICTS OF INTERESTS

The authors declare no conflict of interest

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