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Nanomaterial strategies for mitigating protein misfolding and neuroinflammation in neurodegenerative diseases

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ABSTRACT

Neurodegenerative disorders such as Alzheimer's disease are characterized by pathological protein misfolding, persistent neuroinflammation, and progressive synaptic deterioration. Nanoscale therapeutic platforms offer a versatile strategy for simultaneously suppressing pathogenic protein aggregation and modulating glial hyperactivation, thereby addressing the multifactorial nature of neurodegenerative pathology. Engineered AuNPs, carbon-based nanodots, and related constructs with negatively charged surfaces exhibit high affinity for amyloidogenic peptides, thereby limiting amyloid-β or tau fibrillization, while photothermal strategies using graphene or gold nanorods induce localized thermal disruption of preformed aggregates, enhancing their disassembly. In parallel, functionalized nanocarriers facilitate brain-targeted delivery of anti-inflammatory agents by leveraging receptor-mediated transcytosis or biomimetic cell membrane-camouflaging strategies, attenuating proinflammatory cytokines and promoting autophagic clearance. *In vitro* and *in vivo* models demonstrate integrated therapeutic benefits, including attenuation of plaque deposition, preservation of neuronal integrity, and recovery of cognitive performance. Despite remaining challenges in large-scale synthesis and long-term safety, evolving nanotechnologies offer a flexible and integrated platform capable of disrupting the pathogenic cycle linking protein misfolding, neuroinflammation, and disease progression.

Keywords: Nanomaterial; Protein misfolding; Neuroinflammation; Alzheimer's disease

INTRODUCTION

Advances in nanomedicine have enabled the development of multifunctional platforms capable of targeting key pathological drivers of neurodegenerative disorders, particularly protein aggregation and chronic neuroinflammation. This review presents an integrated overview of dual-action nanotherapeutic strategies, emphasizing recent innovations that exploit surface chemistry to influence both amyloidogenic interactions and glial reactivity. In contrast to previous frameworks that addressed these mechanisms separately, the current synthesis highlights a unified approach to disrupt the pathological feedback loop that sustains neuronal damage.

Nanomaterial-based approaches have emerged as promising strategies to address the dual challenges of misfolded proteins and persistent neuroinflammation in neurodegenerative disorders such as Alzheimer's disease (AD) (Kinney et al., 2018; Song et al., 2014). Progressive accumulation of misfolded amyloid-β (Aβ) and hyperphosphorylated tau results in the formation of neurotoxic aggregates that impair synaptic function, promote oxidative stress and trigger sustained activation of microglia and astrocytes (Figure 1) (Chien et al., 2013; Coomaraswamy et al., 2010; Stefani, 2010; Zhang et al., 2024a). Functional nanoplatforms engineered for enhanced biocompatibility and blood-brain barrier (BBB) penetration have been developed to simultaneously interfere with aggregation pathways and attenuate inflammatory signaling cascades (Gregoretti et al., 2004; Ouyang et al., 2022a). For example, inhibition of Aβ fibrillization has been achieved using negatively charged gold NPs (AuNPs), graphene oxide (GO), and carbon dots, which selectively adsorb monomeric peptides and impede their nucleation into oligomeric and fibrillar assemblies (Liao et al., 2012; Yu et al., 2012; Zhao et al., 2019). Complementary approaches harness photothermal conversion, whereby gold nanorods, nanostars, or graphene-based constructs generate localized heating under near-infrared (NIR) laser irradiation to destabilize preformed Aβ fibrils and promote their disassembly

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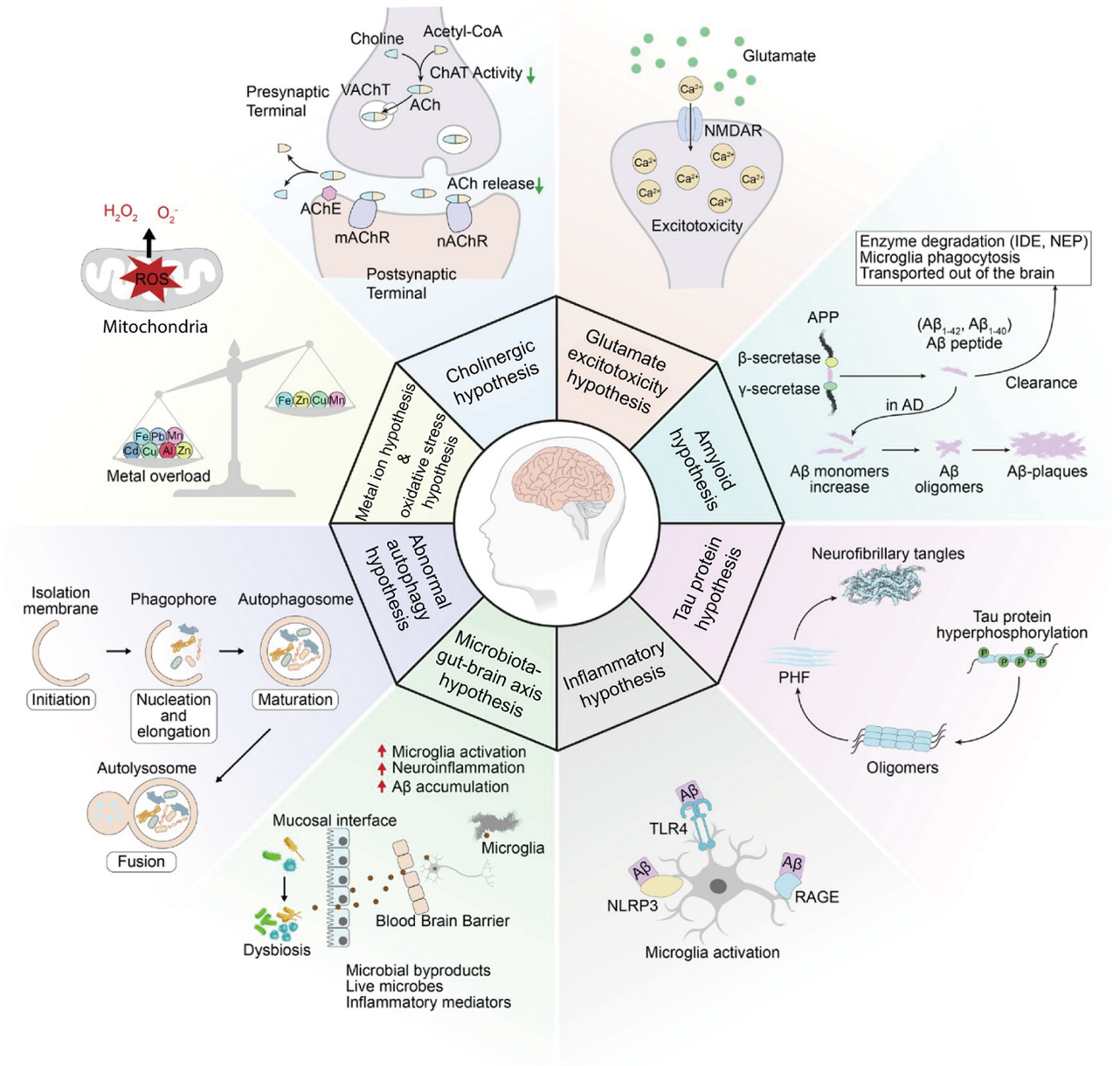

Figure 1 Visual overview of Alzheimer's disease pathogenesis highlighting key contributing mechanisms

Current models implicate multiple, potentially interacting pathways, including the cholinergic hypothesis (acetylcholine deficiency), glutamate excitotoxicity hypothesis (excessive glutamate signaling), amyloid hypothesis (Aβ plaque formation), tau protein hypothesis (neurofibrillary tangles), inflammatory hypothesis (chronic neuroinflammation), microbiota-gut-brain axis hypothesis (gut dysbiosis effects), oxidative stress hypothesis (ROS damage), metal ion hypothesis (metal accumulation), and abnormal autophagy hypothesis (impaired cellular clearance) (Zhang et al., 2024a).

(Lin et al., 2016; Ruff et al., 2018; Triulzi et al., 2008). Comparable strategies have been extended to pathological tau, whose hyperphosphorylation drives aggregation into neurofibrillary tangles that impair cytoskeletal integrity. By functionalizing nanoparticles with peptides specific to tau's amyloid-forming domains, these systems can either interfere with tau aggregation or, when coupled with photothermal properties, promote the disassemble of mature filaments, highlighting the versatility of nanomaterial-based therapeutics (Huang et al., 2015; Jin et al., 2021; Luo et al., 2020).

Chronic glial activation intensifies neuronal injury through sustained release of proinflammatory cytokines, prompting parallel efforts to attenuate inflammatory signaling alongside proteotoxic stress (Singh, 2022; Thawkar & Kaur, 2019; Zhao et al., 2018). Nanoplatforms have been increasingly refined to enhance penetration of the BBB through surface modifications with peptides or receptor ligands that engage endothelial transport pathways, enabling efficient delivery to the central nervous system (CNS) (Alserihi et al., 2022; Ashraf et al., 2015; Cai et al., 2020). Liposomes and polymeric NPs that deliver both aggregation inhibitors and anti-inflammatory compounds have demonstrated synergistic efficacy, simultaneously disrupting Aβ and tau misfolding while mitigating glial-driven pathology (Agyare et al., 2008; Akel et al., 2020; Carpentieri et al., 2012). Incorporation of redox- or pH-sensitive elements enables site-selective cargo release within inflamed or protein-rich microenvironments, thereby improving the spatial precision of therapeutic delivery. In

preclinical AD models, nanocarriers not only sequester misfolded proteins through surface adsorption to facilitate microglial phagocytosis but also shift glial states toward neuroprotective phenotypes through co-delivery of anti-inflammatory compounds (Carpentieri et al., 2012; Ouyang et al., 2022b; Qian et al., 2022). To mitigate systemic toxicity and improve pharmacokinetics, biomimetic coatings, biocompatible polymers, and biodegradable shells have been employed to prolong circulation, facilitate BBB crossing, and trigger controlled drug release under disease-specific oxidative or enzymatic conditions (Chen et al., 2014; Xia et al., 2019; Zamora-Justo et al., 2019). However, substantial challenges remain, particularly in achieving large-scale, reproducible fabrication of multifunctional nanostructures and optimizing dosing within the narrow physiological constraints imposed by BBB permeability and neuroinflammatory sensitivity. Even so, the ability to integrate complementary therapeutic strategies into a single targeted platform—supported by advances in biomimetic coatings, peptide engineering, and stimulus-responsive release—continues to highlight the therapeutic promise of nanotechnology for AD and related neurodegenerative disorders.

This review examines how targeted nanomaterials simultaneously engage two interdependent pathological processes central to neurodegenerative progression: misfolded protein accumulation and persistent neuroinflammation. Aggregated forms of Aβ, tau, and α-synuclein contribute not only to direct neuronal injury but also to prolonged glial activation and oxidative stress (Alcendor et al., 2012; Chien et al., 2013; Coomaraswamy et al., 2010). By engineering NPs—often coated with peptides or cell membranes to penetrate the BBB—researchers can disperse or inhibit the formation of toxic protein fibrils while simultaneously delivering anti-inflammatory drugs (Agyare et al., 2008; Kumar & Pruthi, 2014; Ouyang et al., 2022b). These dual-action platforms, such as gold and carbon-based nanomaterials optimized for photothermal disruption of fibrils or loaded with agents such as rapamycin, enable coordinated modulation of proteostasis and immune tone, leading to reductions in cytokine burden and preservation of neuronal viability (Huang et al., 2015; Jin et al., 2021; Song et al., 2014). Integration of biomimetic and stimuli-responsive features further enhances drug release selectivity within inflamed or aggregate-rich microenvironments, minimizing off-target exposure and systemic toxicity. Although challenges persist in large-scale synthesis and long-term safety validation, these multifaceted nanotherapeutics represent considerable promise for slowing disease progression more effectively than single-target interventions.

PATHOPHYSIOLOGY OF PROTEIN MISFOLDING AND NEUROINFLAMMATION

Aberrant protein folding and chronic neuroinflammation intersect as central determinants of neurodegenerative pathology, exemplified in AD, where extracellular Aβ plaques and intracellular tau tangles drive persistent activation of microglia and astrocytes (Rajmohan & Reddy, 2017; Su et al., 2010). Activated microglia and astrocytes release a cascade of proinflammatory cytokines and reactive oxygen species (ROS), accelerating synaptic dysfunction and amplifying the burden of neurotoxic protein deposits (Di Benedetto et al., 2022; Huang et al., 2021; Wang et al., 2015). Inflammatory signaling simultaneously impairs proteostatic control by disrupting autophagic flux and endoplasmic reticulum homeostasis, producing additional misfolded proteins and reinforcing the pathogenic cycle. This reciprocal amplification poses a formidable clinical challenge, requiring delivery systems that bypass physiological barriers, selectively target noxious aggregates, and suppress inflammatory mediators that exacerbate neuronal injury.

Nanomaterial-based therapeutics offer a promising multi-level intervention strategy by restoring proteostatic balance, mitigating excessive neuroinflammation, and improving neuropathological outcomes. These platforms can be functionalized to enhance clearance of misfolded protein aggregates by targeting specific pathogenic hallmarks, such as Aβ oligomers, and incorporating small-molecule modulators of autophagy to promote intracellular degradation of misfolded species. For example, rapamycin, a well-established autophagy enhancer with limited brain penetration, has been successfully encapsulated within hybrid nanocarriers capable of traversing the BBB and inducing autophagic pathways in neuronal populations, thereby facilitating clearance of early-stage aggregates before they evolve into fibrillar deposits (Yang et al., 2022).

Targeting neuroinflammation also represents a critical dimension of therapeutic intervention. Under sustained exposure to misfolded protein assemblies, microglia adopt a proinflammatory phenotype that contributes to neuronal degeneration. Nanomaterial-based systems have been designed to moderate this process by reprogramming glial activation and suppressing inflammatory signaling (Lu et al., 2019; Zeng et al., 2018). For example, NPs encapsulating soluble epoxide hydrolase inhibitors have been shown to reduce cytokine release and limit glial hyperactivation, thereby protecting neurons from secondary damage caused by excess cytokines and ROS (Ghosh et al., 2020).

The functional architecture of these NPs is strategically tailored to overcome key physiological and pathological barriers. Core design objectives include enhancing translocation across the BBB, achieving selective recognition of aggregated protein species and site-specific inflammatory cues, and minimizing off-target effects (Alserihi et al., 2022; Ashraf et al., 2015; Welge et al., 2009). Some platforms incorporate cell membrane coatings derived from platelets or other endogenous sources, exploiting their immune-evasive characteristics to evade phagocytic clearance, prolong systemic circulation, and facilitate delivery to diseased tissue (Han et al., 2022; Tao et al., 2022). Others, such as cerium oxide (CeO_2)-based NPs, leverage their intrinsic antioxidant and multi-enzyme-like properties to scavenge ROS and lower oxidative stress, attenuating a principal driver of neuroinflammation (Kim et al., 2012; Kwon et al., 2016; Singh et al., 2011). By dampening oxidative cascades, these nanomaterials preserve synaptic architecture, reduce neuronal vulnerability, and interrupt stress-induced pathways that exacerbate protein misfolding and aggregate propagation. Additional strategies incorporate photothermal or photodynamic components into nanocarriers that, upon external stimulation, generate heat or reactive molecules capable of destabilizing protein aggregates in regions of pathological accumulation (Bastús et al., 2011; Yin et al., 2016). However, strategies that promote protein disassembly or release must be coupled with effective binding or degradative motifs–such as robust chemistries functionalities

or peptidic fragments–to safely sequester or eliminate liberated protein species to prevent reaggregation. In parallel, nanoplatforms incorporating metal-chelating ligands can help restore metallic homeostasis in neurodegenerative by capturing excessive iron, copper, or zinc, thereby disrupting metal-induced protein aggregation and attenuating oxidative stress to further safeguard neurons (Ciccotosto et al., 2003; Kepp, 2012; Liu et al., 2006).

Targeted modulation of glial activity is critical for reinforcing nanotherapeutic strategies aimed at interrupting neurodegenerative cascades (Heneka et al., 2015). NPs have been developed to deliver short interfering RNA and related nucleic acid constructs that inhibit key inflammatory mediators within microglia, thereby constraining excessive cytokine production and downstream neurotoxicity (Lazar et al., 2013; Li et al., 2016; Liu et al., 2020a). Complementary designs incorporate bioactive peptides that drive microglia toward a protective phenotype, enhancing phagocytic clearance of misfolded proteins while limiting generation of neurotoxic intermediates (Liu et al., 2021; Zhang et al., 2023; Zhao et al., 2018). Such approaches are particularly relevant during advanced disease stages, where glial populations remain locked in a persistent inflammatory state and exhibit reduced capacity for aggregate removal. Redirecting microglial function away from inflammatory amplification and toward efficient proteopathic clearance reduces the formation of secondary aggregates and dampens localized inflammatory signaling that sustains neuronal injury. In parallel, integration of small-molecule therapeutics with engineered NP frameworks has enabled effective circumvention of BBB restrictions. Surface modifications, including polyethylene glycol coatings, cell-penetrating peptides, and receptor-specific ligands, promote uptake within diseased brain regions and permit controlled release of autophagy modulators, inhibitors of proinflammatory enzymes, or agents that sequester toxic protein species. These co-delivery architectures have yielded superior outcomes in preclinical models, with concurrent reductions in aggregate burden and chronic neuroinflammation, underscoring the capacity of precisely engineered nanosystems to unify multiple therapeutic modalities and amplify overall disease-modifying efficacy.

Although nanomaterial-based interventions continue to evolve, their capacity to simultaneously target multiple pathological processes aligns with the mechanistic complexity of neurodegenerative diseases. By simultaneously boosting misfolded protein clearance and preventing runaway inflammatory responses, these therapies diverge from conventional single-target approaches. With continued development, increasing attention will focus on optimizing biocompatibility, regulatory safety, and scalable manufacturing. Nonetheless, demonstrated efficacy in preclinical models, including reduction of proteotoxic burden and reestablishment of immune homeostasis, indicates that these nanoengineered platforms can disrupt the self-reinforcing cycle of misfolded protein aggregation and persistent inflammation. This emerging therapeutic paradigm offers a compelling strategy for altering the course of neurodegenerative diseases considered intractable under conventional treatment.

Aberrant aggregation of Aβ, tau, and α-synuclein initiates a cascade of neuroinflammatory responses that accelerate neuronal dysfunction and reinforce proteopathic progression (Du et al., 2010; Pereira et al., 2019; Shaw et al., 2009). As these proteins transition into oligomeric and fibrillar assemblies, they activate microglia and astrocytes to release proinflammatory cytokines and chemokines that further destabilize neural circuits (Di Benedetto et al., 2022; Wang et al., 2015, 2018a). This pathogenic cycle of inflammation and immune activation exacerbates neuronal damage and fosters further protein aggregation. In AD, soluble Aβ oligomers and fibrils induce reactive gliosis, shifting glial populations toward proinflammatory states marked by elevated secretion of interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) (Ho et al., 2005; Lue et al., 2001; Wang et al., 2018b). Similar processes occur in other neurodegenerative conditions involving protein misfolding, fostering a microenvironment conducive to chronic inflammation and sustained aggregate formation. Therapeutic disruption of this glia-protein interaction axis has thus emerged as a central objective in mitigating neurodegenerative pathologies, as reductions in cytokine storms and glial overactivation can prevent long-term neuronal network deterioration. Strategies that degrade neurotoxic aggregates while delivering anti-inflammatory agents or chemokine receptor antagonists aim to dismantle the self-perpetuating cycle of misfolded proteins and inflammation. Preclinical evidence increasingly supports the superiority of interventions that incorporate both neuropathological and immunological therapeutic endpoints over approaches that isolate a single molecular target. By attenuating the inflammatory triggers initiated by Aβ, tau, and α-synuclein accumulation, such interventions hold potential to reprogram disease trajectories rather than merely delay symptom progression.

Sustained neuroinflammation acts as a potent accelerator of proteostatic failure in neurodegenerative disorders, exacerbating misfolding and aggregation of Aβ, tau, and α-synuclein. Persistent activation of microglia and astrocytes drives continuous release of proinflammatory cytokines, chemokines, and ROS, resulting in neuronal injury and progressive impairment of protein clearance pathways (Di Benedetto et al., 2022; Huang et al., 2021; Wang et al., 2015). Evidence indicates that inflammatory effects extend beyond neural parenchyma to the cerebrovascular interface. Notably, Aβ oligomers and seeds disrupt vascular endothelial-cadherin junctions in human brain microvascular endothelial cells prior to overt inflammatory activation, compromising barrier integrity at an early disease stage (Li et al., 2024a). This increase in endothelial permeability not only primes the brain for oxidative and inflammatory insults but also perpetuates a feedback loop in which misfolded proteins amplify inflammation, which, in turn, accelerates further aggregation. *In vitro* and *in vivo* assays consistently demonstrate that vascular dysfunction and inflammatory signaling converge to promote proteotoxic accumulation, establishing early conditions favorable to disease progression. Under physiological conditions, autophagy and enzymatic degradation limit exposure to misfolded proteins; however, chronic glial activation overwhelms these protective mechanisms (Caccamo et al., 2010). Accumulation of Aβ, tau, and α-synuclein disrupts autophagic flux, impairs lysosomal trafficking, and alters chaperone regulation, further destabilizing neuronal proteostasis (Caccamo et al., 2010; Coomaraswamy et al., 2010; Faustino et al., 2017). Environmental and cellular studies reinforce this interaction, revealing that metal-rich NPs containing iron, aluminum, or titanium co-localize with hyperphosphorylated tau, α-synuclein, and TDP-43 in the

substantia nigra of young urban residents, exacerbating aggregation-prone states (Calderón-Garcidueñas et al., 2020). Similarly, silica dioxide NPs promote α-synuclein aggregation, triggering membrane leakage, caspase activation, and ROS production (Pang et al., 2021). Collectively, these findings position neuroinflammation as a central mechanistic amplifier of pathological protein misfolding in AD, Parkinson's disease (PD), and related neurodegenerative disorders (Misrani et al., 2021), where compromised endothelial integrity, chronic glial activation, and environmental NP exposure converge to drive oxidative damage and proteopathic burden.

RATIONALE FOR NANOMATERIALS IN TARGETING PROTEIN MISFOLDING AND NEUROINFLAMMATION

Therapeutic strategies aimed at mitigating protein misfolding and neuroinflammation in neurodegenerative disorders require delivery systems capable of penetrating the BBB, minimizing systemic exposure, and selectively modulating disease-relevant molecular targets. Nanomaterials engineered for these applications can exhibit favorable pharmacological properties, including protection of labile therapeutics from premature degradation, controlled and site-specific release, and surface functionalization that enhances affinity for pathological protein assemblies. In disorders, such as Alzheimer's disease, where amyloid and tau accumulation disrupt vascular integrity and neural architecture, overcoming the restrictive BBB remains a critical translational challenge (Huang & Mucke, 2012; Krol et al., 2013). NPs optimized for size, surface charge, and ligand targeting can exploit receptor-mediated transcytosis or transient tight-junction openings to shuttle cargo into affected brain areas. Directing nanocarriers toward aggregation-prone loci enhances therapeutic selectivity and reduces off-target deposition.

Following translocation into the CNS, nanotherapeutic systems must engage pathologic substrates with spatial precision. Smart nanocarriers are designed to respond to microenvironmental cues—including elevated ROS, reduced pH, or aberrant protease activity—enabling on-demand release of therapeutic cargo specifically at lesion sites. This stimuli-responsive approach limits systemic toxicity while sustaining local treatment efficacy against both protein aggregates and inflammatory mediators. Additional external activation modalities, such as photothermal and ultrasound triggers, further enhance spatiotemporal control over drug delivery, ensuring healthy tissue remains protected. Peripheral interventions, such as NPs that sequester circulating misfolded proteins or modulate systemic immune responses, further highlight the capacity of nanoengineered systems to mitigate complex neurodegenerative processes (Huang et al., 2015; Jin et al., 2021; Song et al., 2014).

Surface functionalization plays a critical role in optimizing biocompatibility, pharmacokinetics, and uptake within damaged regions of the CNS. Biomimetic coatings derived from cellular membranes, including platelets, erythrocytes, and engineered cell lines, have been shown to reduce immunogenicity, extend systemic circulation, and preferentially localize NPs to inflamed or injured vasculature (Jokerst et al., 2011; Xia et al., 2019; Zamora-Justo et al., 2019). Platelet membrane-coated NPs, for example, retain endogenous adhesion ligands that bind selectively to sites of vascular injury—a key feature in microvascular pathology associated with various neurodegenerative proteinopathies. Polyethylene glycol (PEG) functionalization similarly prolongs NP half-life by reducing immunorecognition and nonspecific protein adsorption, while enabling targeted delivery through conjugated peptides that recognize Aβ fibrils or inflammation-associated receptors (Jokerst et al., 2011; Xia et al., 2019; Zamora-Justo et al., 2019). These approaches collectively optimize selective accumulation in disease foci while minimizing off-target complications.

Therapeutic efficacy is further improved through co-encapsulation of synergistic agents that concurrently address protein aggregation and neuroinflammatory signaling. Because proteotoxicity arises from both toxic protein assemblies and glial-driven inflammation, platforms combining autophagy inducers with anti-inflammatory compounds often surpass the performance of single-pathway interventions. Encapsulation stabilizes these agents, enables controlled and sustained release, and facilitates coordinated modulation of aggregation, inflammation, and oxidative stress within a unified nanocarrier system (Kumari et al., 2022). Cell membrane-coated liposomes exemplify this strategy, demonstrating prolonged circulation, selective targeting of inflamed cerebral microvasculature, and effective delivery of dual therapeutics—such as rapamycin combined with small-molecule inhibitors of inflammatory mediators—in AD models. By tuning membrane protein composition, nanocarriers can be directed to early-stage lesions, enhancing local clearance of pathogenic aggregates.

A variety of nanomaterial platforms, including polymeric NPs, lipid-based carriers, mesoporous inorganic scaffolds, and metal oxide cores, support sustained or stimulus-responsive drug release. Certain metal-based nanostructures also exhibit intrinsic antioxidant properties, directly scavenging ROS and mitigating oxidative stress that accelerates protein misfolding and neuronal damage (Jiang et al., 2022; Kepp, 2012; Surnar et al., 2018). To minimize toxicity and improve biocompatibility, recent designs increasingly favor biodegradable polymers and biologically derived membranes that reduce immune activation and facilitate efficient clearance. Parallel advances in manufacturing standardization have improved scalability and batch-to-batch consistency, preserved surface functionality, and enabled reproducible drug encapsulation and release profiles. Together, these innovations integrate precise brain delivery, selective engagement of pathological cascades, and tailored therapeutic release to counteract neurodegenerative progression and preserve neuronal integrity.

Nanomaterial design strategies for CNS delivery

Effective delivery of nanomaterials to the CNS requires precise control over physicochemical parameters, particularly size, surface charge, and chemical composition, to successfully traverse the BBB (Alserihi et al., 2022; Ashraf et al., 2015). Nanocarriers exceeding several hundred nanometers tend to accumulate in reticuloendothelial organs such as the liver and spleen, whereas ultrasmall structures risk rapid clearance through renal filtration (Blanco et al., 2015; Sumbayev et al., 2013). Optimal CNS delivery is typically achieved with carriers in the 5–200 nm range, which retain sufficient cargo capacity and exhibit favorable biodistribution within cerebral microvasculature. Surface charge is another critical determinant of BBB translocation efficiency. Positively charged systems enhance membrane interactions but heighten toxicity and clearance, whereas neutral or slightly negative surfaces prolong circulation by

reducing nonspecific binding. The inclusion of hydrophobic or aromatic domains may promote opsonization and plasma protein binding, emphasizing the importance of surface stability and stealth features for maximizing brain uptake. Targeted delivery strategies frequently exploit receptor-mediated transcytosis mechanisms, using ligands for transferrin, insulin, lactoferrin, or low-density lipoprotein receptors to shuttle ligand-bound nanocarriers across endothelial layers (Chen et al., 2010). However, competition with endogenous ligands can limit transport efficiency. An alternative strategy involves the use of focused ultrasound in combination with circulating microbubbles to transiently disrupt tight junctions, facilitating targeted nanomaterial entry without lasting vascular damage. Additionally, disease-related BBB alterations—such as junctional loosening or receptor up-regulation—may enhance nanomaterial transport, albeit with potential off-target risks (Loeck et al., 2023). Collectively, these approaches underscore the complex interplay among nanocarrier geometry, surface chemistry, and active targeting in achieving efficient BBB entry (Table 1).

Surfactant-based approaches have significantly enhanced nanocarrier stability, prolonged systemic circulation, and improved CNS uptake by modulating NP-cell interactions and reducing opsonization. For example, kaempferol-loaded solid lipid NPs (K-SLNs) formulated with stearic acid and polysorbate 80 (451.2 nm) achieved 84.92% entrapment efficiency and released 93.24% of the drug *in vitro*, ultimately reducing ischemic brain injury in rats (Ghosh et al., 2024). Another formulation employing a yeast cell wall-derived carrier coated with polysorbate 80 and loaded with dextromethorphan (187.25±73.37 nm, +4.3 mV) exhibited low hemolytic potential and significantly attenuated neuroinflammatory markers (Valizadeh et al., 2025). Piperine-encapsulated chitosan-lipid NPs attained over 85% drug loading and sustained release for 24 h, improving cognitive function in diabetic rats by mitigating oxidative stress (Darwish et al., 2024a). Similarly, a chitosan-based icariin nanocomposite up-regulated synaptic markers and suppressed neuroinflammation in a vascular dementia model (Li et al., 2024b), while curcumin-selenium-poly(lactic-co-glycolic acid) (PLGA) NPs lowered Aβ burden and improved memory in AD models (Huo et al., 2019). A rod-shaped polystyrene NP functionalized with anti-VCAM-1 exhibited 2.5-fold greater endothelial adhesion under static conditions compared to its spherical equivalent, underscoring

Table 1 Nanoparticle-based strategies for CNS delivery

Approach	Nanocarrier type	Therapeutic agent	Targeting strategy	References
Gabapentin-loaded Nanospray Dried Chitosan NPs	Chitosan NP	Gabapentin (GBP)	Intranasal administration; Nanospray drying	Salama et al., 2021
Piperine-loaded Chitosan Lipid NPs (PP-CLNPs)	Chitosan-lipid NP	Piperine (PP)	Oral delivery; Adjuvant to Metformin	Darwish et al., 2024a
Erythrocyte Membrane-Camouflaged COF	COF	Bindarit	Erythrocyte membrane coating; pH-responsive release	Yang et al., 2026
2-Deoxy-Glucose Functionalized Dendrimer (2DG-D)	Dendrimer	Pioglitazone (Pio)	2-Deoxy-glucose (2DG) functionalization for neuronal targeting	Dhull et al., 2024
Hydroxyl-terminated PAMAM Dendrimers	Dendrimer	N/A (size-effect study)	Intrinsic targeting; Size variation (G4 vs G6)	Liaw et al., 2020
Catalase-loaded Exosomes (exoCAT)	Exosome	Catalase	Intranasal delivery; Inherent exosome targeting	Haney et al., 2015
Designer Exosomes via EXOtic Devices	Exosome	Catalase mRNA	Genetically encoded devices for mRNA packaging and delivery	Kojima et al., 2018
Gold-labeled MSC-derived Exosomes (MSC-exo)	Exosome	AuNPs (label)	Intranasal; Inflammation-driven homing	Perets et al., 2019
Cell-derived Extracellular Vesicles (EVs)	Extracellular vesicle	N/A (carrier property study)	Inherent properties of parent cells	Haney et al., 2021
LDE-Methotrexate (LDE-MTX)	Lipoprotein-like NP	Methotrexate (MTX)	Intrinsic uptake in ischemic tissue	Pereira et al., 2025
Platelet/CCR2-Cell Hybrid Membrane-Coated Liposomes	Liposome	Two unspecified drugs	Hybrid membrane from platelets and CCR2-overexpressing cells	Lin et al., 2024
Hybrid Membrane-Coated Liposome (PP@PCL)	Liposome	Paeonol, Polymetformin	4T1 tumor cell/platelet hybrid membrane	Tang et al., 2024
Lf-functionalized LNPs	LNP	α-Mangostin, BACE1 siRNA	Intranasal delivery; Lactoferrin receptor targeting	Xu et al., 2025
Borneol-modified Lipid NP Nasal Spray (BLNP-NS)	LNP	N/A (delivery study)	Intranasal spray; Borneol modification	Wang et al., 2024a
Magnetic Nanocarrier with FUS	Magnetic NP	15d-PGJ2 (PPARγ agonist)	Magnetic targeting with focused ultrasound (FUS) enhancement	Wang et al., 2023c
Mesoporous Levodopa Nanoformulations	Mesoporous NP	Levodopa	Intrinsic interaction with α-synuclein	Guo et al., 2024
Kynurenic Acid-loaded Micelles (KYNA-MICs)	Micelle	Kynurenic acid (KYNA)	Micellar formulation for BBB penetration	Chen et al., 2024
Platelet/Microglia Hybrid Membrane-Coated Nanocrystals	Nanocrystal	Cyclosporine A (CsA)	Platelet and microglia hybrid membrane coating	Zhou et al., 2025b
Biomimetic Self-Propelled Nanomotor	Nanomotor	Curcumin	Macrophage membrane coating; MnO2-catalyzed self-propulsion	Ye et al., 2024
RvD2-loaded Neutrophil Membrane Nanovesicles	Nanovesicle	Resolvin D2 (RvD2)	Neutrophil membrane coating	Dong et al., 2019
Andrographolide-loaded NLCs (AndroNLCs)	NLC	Andrographolide (Andro)	Oral administration; enhanced GI stability	Lapmanee et al., 2025
Levosulpiride-loaded NLCs (LEVO-NLCs)	NLC	Levosulpiride	NLC formulation for enhanced brain delivery	Maqsood et al., 2022

Continued

Approach	Nanocarrier type	Therapeutic agent	Targeting strategy	References
Nerolidol-loaded NLCs (NR-NLC)	NLC	Nerolidol (NR)	NLC formulation for enhanced brain delivery	Iqubal et al., 2020
LNT M2 Macrophage Scaffold with PTX NPs	NP in hydrogel	Paclitaxel (PTX)	Injectable Liquid nitrogen-treated M2 macrophage (LNT M2) scaffold	Lu et al., 2025
Co-administered PLGA NPs	PLGA	Elvitegravir (EVG), Curcumin (CUR)	Passive targeting via small particle size (<140 nm)	Godse et al., 2025
Macrophage Exosome-PLGA Hybrid NPs (CMC-EXPL)	PLGA	Celastrol, Minocycline	Macrophage-derived exosome functionalization	Lv et al., 2024
Auranofin-loaded PLGA NPs	PLGA	Auranofin	Oral administration nanoformulation	Kushawaha et al., 2024
Curcumin/Selenium Co-loaded PLGA Nanospheres	PLGA	Curcumin, Selenium NPs	Intrinsic binding to Aβ plaques	Huo et al., 2019
EGCG-loaded PEGylated-PLGA NPs	PLGA	Epigallocatechin-3-gallate (EGCG)	PEGylation for enhanced brain delivery	Cano et al., 2018
Necrosis-Targeted PLGA NPs	PLGA	800CW (imaging agent)	800CW ligand targeting necrotic cells	Cruz et al., 2016
Icariin-PEG-PLGA NPs in Chitosan Hydrogel	PLGA in hydrogel	Icariin (Ica)	Intranasal delivery	Li et al., 2024d
Microglial Membrane-Coated PDA NPs (PDA-Mem@M)	Polydopamine NP	Memantine	Microglial membrane coating for microglial targeting	Jiang et al., 2025
Melanoma Cell Membrane-Camouflaged NPs	Polymeric NP	2-Methoxyestradiol (2ME2)	B16F10 melanoma cell membrane coating; ROS-responsive	Xia et al., 2024
Neutrophil-targeting Dendrigraft Poly-L-lysine (DGL) NPs	Polymeric NP	Catalase	PGP tripeptide ligand for neutrophil targeting	Zhang et al., 2017
Modified Low Molecular Weight PEI Polyplexes	Polyplex	Plasmid encoding CD200 gene	Cross-linking with succinic acid for BBB crossing	Nouri et al., 2017
Anti-VCAM-1 Coated Rod-shaped NPs	Polystyrene NP	N/A (targeting study)	Anti-VCAM-1 antibody; Geometric shape	Da Silva-Candal et al., 2019
Aβ-peptide Engineered Prussian Blue NPs	Prussian blue NP	Curcumin, miRNA-124	Aβ-derived peptide (CKLVFFAED) engineering	Song et al., 2025
Transferrin-modified Mesoporous Selenium Nanoflowers	Selenium NP	Metformin (Met)	Transferrin (Tf) modification for receptor-mediated transport	Guo et al., 2025
Chitosan-Coated Solid Lipid NPs (CS-coated SLNs)	SLN	Carbenoxolone (CBX)	Intranasal delivery; Chitosan mucoadhesive coating	Nematalla et al., 2025
Crocin-loaded Solid Lipid NPs (SLNC)	SLN	Crocin	Oral administration for enhanced bioavailability	Kakebaraei et al., 2024

the synergistic impact of geometry and surface functionalization on CNS delivery (Da Silva-Candal et al., 2019).

Intranasal delivery presents a non-invasive route that bypasses systemic metabolism and exploits the olfactory and trigeminal pathways for direct brain access. In a parkinsonian rat model, chitosan-coated solid lipid NPs encapsulating carbenoxolone (164±0.12 nm, ~98% entrapment) significantly elevated dopamine levels and reduced α-synuclein accumulation, outperforming standard treatments (Nematalla et al., 2025). Similarly, lipid NPs (98.25 nm) encapsulating crocin with 98.33% efficiency attenuated oxidative damage and improved cognitive function in a pentylenetetrazol-induced seizure model (Kakebaraei et al., 2024). A borneol-modified lipid NP nasal spray achieved an outlet deposition fraction of 23.58% and ameliorated chronic migraine symptoms in rats (Wang et al., 2024a). Another system utilized a ROS-responsive “padlock” NP cloaked in melanoma cell membranes to deliver 2-methoxyestradiol intranasally, effectively mitigating neuroinflammation (Xia et al., 2024). Additionally, magnetically guided intravenous administration combined with focused ultrasound enhanced targeted transport of PPARγ agonist-loaded nanocarriers (15d-PGJ2-MNPs), reducing astroglial proliferation and promoting hematoma resolution following hemorrhagic stroke (Wang et al., 2023a). In a microfluidic BBB model, catalase-conjugated dendrigraft poly-L-lysine NPs successfully reached ischemic regions, demonstrating that inflammation-guided navigation and nose-to-brain delivery strategies can be deployed in a complementary manner (Zhang et al., 2017).

Biomimetic coatings and hybrid membranes offer a promising approach for achieving BBB penetration without eliciting immune responses (Gregoretti et al., 2004; Sahni et al., 2011). Exosomes—endogenous vesicles enriched with transmembrane proteins—and synthetic carriers cloaked in exosome-mimetic lipid layers exploit physiological uptake pathways to reduce immune recognition. Similarly, cell membrane-coated nanocarriers enhance tissue-specific targeting; for instance, platelet membranes bind selectively to inflamed vasculature, while CCR2-enriched coatings direct carriers to sites of chronic inflammation, a hallmark of many neurodegenerative diseases (Han et al., 2022; Tao et al., 2022; Xia et al., 2019). Hybrid systems incorporating autophagy-enhancing agents such as rapamycin or TPPU within CCR2-engineered platelet-coated NPs demonstrate preferential accumulation in inflamed neural regions and attenuation of neuroinflammation through modulation of autophagic flux (Figure 2) (Lin et al., 2024). Stimulus-responsive nanocarriers composed of biodegradable polymers or phospholipids further refine drug release profiles by responding to microenvironmental cues such as pH shifts or disease-associated enzymatic activity. These platforms facilitate localized, controlled release of agents like rapamycin, aiding the degradation of amyloid plaques in AD (Chauhan, 2018; Kamaly et al., 2016; Wu et al., 2015). Chemotactic targeting strategies exploiting CCR2 signaling enhance BBB penetration under inflammatory conditions while minimizing peripheral immune activation. Sustained-release systems, including liposomes and polymeric spheres, maintain therapeutic concentrations within disease foci, simultaneously

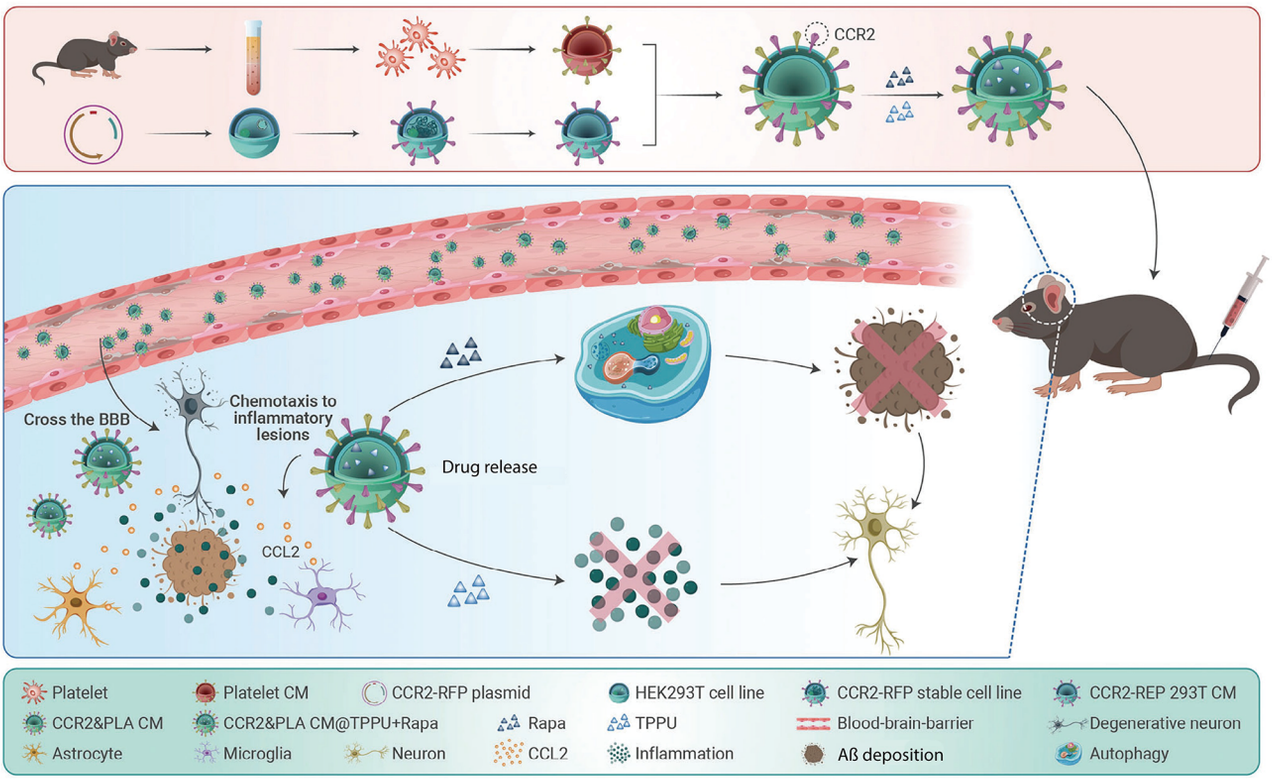

Figure 2 Schematic of the fabrication and therapeutic application of drug release hybrid cell membrane liposomes for Aβ deposition

Platelet membranes were isolated from retro-orbital blood samples collected from mice, while CCR2-RFP-overexpressing membranes were derived from stably transfected HEK293T cells. The two membrane types were fused to generate hybrid vesicles, which were subsequently loaded with rapamycin and TPPU. After intravenous administration, these hybrid membrane liposomes preferentially accumulated at inflammatory lesions within the CNS, where localized cargo release enhanced autophagy, attenuated neuroinflammation, and conferred therapeutic benefits in AD models (Lin et al., 2024).

mitigating inflammation and supporting plaque degradation. Co-administration of rapamycin and TPPU has proven effective in targeting both proteotoxic accumulation and neuroinflammatory dysregulation in preclinical neurodegeneration models (Fan et al., 2018; Lazar et al., 2013; Li et al., 2016).

Advanced biomimetic designs extend beyond immune evasion to actively engage disease-relevant transport pathways. For example, polydopamine NPs coated with microglial membranes target neuroinflammatory regions, delivering memantine to restore synaptic spine density and alleviate depressive symptoms (Jiang et al., 2025). Gelatin methacryloyl scaffolds incorporating M2 macrophage-derived nanocarriers have been used to deliver paclitaxel to reduce glial scarring and improve motor function in spinal cord injury (Lu et al., 2025). Exosome-functionalized PLGA NPs co-loaded with celastrol and minocycline mitigated M1-driven neuroinflammation in post-stroke depression (Lv et al., 2024). Additionally, macrophage membrane-coated NPs embedded with mesoporous SiO_2-manganese dioxide (MnO_2) tentacle structures demonstrated ROS scavenging and M1-to-M2 polarization, providing significant neuroinflammatory relief (Ye et al., 2024). These advancements integrate pharmacokinetic optimization with pathological specificity, advancing precision-targeted therapeutic delivery across the BBB in CNS disorders.

Exosome-based platforms exploit the endogenous trafficking mechanisms of these vesicles, which naturally ferry proteins, lipids, and RNA across cellular barriers. Macrophage-derived exosomes loaded with catalase (100–200 nm) significantly reduced oxidative stress in a PD model (Haney et al., 2015), while engineered EXOtic constructs enhanced exosome production and catalase mRNA transfer into neurons, mitigating neuroinflammation (Kojima et al., 2018). Similarly, bone marrow mesenchymal stem cell-derived exosomes labeled with AuNPs enabled real-time computed tomography tracking, demonstrating preferential localization to inflamed regions rather than healthy tissue (Perets et al., 2019). Dendrimer- and micellar-based nanocarriers also exhibit considerable therapeutic potential, with a 2-deoxy-glucose-conjugated dendrimer shown to target pediatric traumatic brain injury (Dhull et al., 2024) and micelles carrying kynurenic acid (106 nm) shown to protect dopaminergic neurons by mitigating protein aggregates (Chen et al., 2024). Mesoporous or multifunctional carriers integrate features such as ROS scavenging and anti-aggregative activity; for instance, mesoporous levodopa assemblies effectively inhibited α-synuclein aggregation (Guo et al., 2024), while mesoporous selenium NPs releasing metformin enhanced microglial clearance of Aβ (Guo et al., 2025; Sun et al., 2019). Likewise, transferrin-conjugated mesoporous silica NPs exhibited BBB penetration and reduced Aβ aggregates in human brain endothelial cells (Loureiro et al., 2017). A PLGA-based nanoplatform loaded with auranofin (101.5 nm, ~98% encapsulation efficiency) suppressed neuroinflammation and reversed cognitive deficits in an AD model (Kushawaha et al., 2024; Zhao et al., 2018). Raman spectroscopy has verified the molecular integrity of liposomal nanomedicines for glioblastoma and neurodegeneration, enabling noninvasive formulation tracking (Rodà et al., 2023).

Although challenges remain in scalability, reproducibility, and long-term safety, ongoing refinements in biomimetic interfaces, intranasal delivery, surfactant optimization, and multifunctional architectures hold significant potential for personalized CNS nanomedicines.

Nanomaterial interventions for protein misfolding

Nanomaterials have shown considerable promise in disrupting pathogenic protein misfolding associated with neurodegenerative and systemic proteinopathies. Acting as molecular chaperones or therapeutic carriers, NPs can adsorb misfolded proteins, disassemble fibrillar aggregates, and facilitate their clearance through autophagic or proteasomal pathways (de Retana et al., 2019; Fernández-de-Retana et al., 2017; Huang et al., 2014). Metal-based nanostructures, polymeric micelles, and functionalized liposomes employ diverse mechanisms such as electrostatic and hydrophobic interactions or photothermal disaggregation to destabilize aggregates (Cassidy et al., 2020; Singh et al., 2017; Yin et al., 2016). Some platforms incorporate recognition ligands that selectively bind β-sheet–enriched structures, establishing multivalent contacts with fibrils to inhibit oligomer propagation and dismantle existing deposits (Liu et al., 2016; Waku et al., 2020). Repeated administration of such constructs confers sustained neuroprotection, highlighting their potential to arrest disease progression (Table 2).

Metal-based nanomaterials offer key avenues for mitigating pathogenic protein assemblies, with AuNPs being especially versatile due to their tunable surface properties and demonstrated affinity for amyloidogenic peptides such as Aβ and α-synuclein (Gülseren et al., 2024; Li et al., 2024c; Liao et al., 2012; Liu et al., 2023; Thai et al., 2024). Bimetallic Au/Ag formulations exhibit enhanced anti-aggregative activity, achieving 74% inhibition of Aβ fibrillation by binding misfolded peptides, outperforming single-metal systems and indicating synergistic activity (Gülseren et al., 2024). Gold nanospheres and nanorods further enable photothermal disruption of established fibrils, fragmenting deposits into less stable species. Iron oxide NPs provide an alternative strategy by enabling magnetic guidance toward regions enriched in misfolded proteins when conjugated with antibodies or peptides, while incorporation of copper- or zinc-chelating ligands allows these platforms to neutralize metal-driven aggregation processes that contribute to AD pathology (Cheng et al., 2015a; Gao et al., 2020a; Hu et al., 2015). Chiral metal NPs have also demonstrated dose-dependent reductions in Aβ fibrillation, with molecular dynamics simulations indicating that 5 nm AuNPs can neutralize acidic domains of α-synuclein and block fibrillogenesis (Li et al., 2024c; Liao et al., 2012; Liu et al., 2023; Palmal et al., 2014; Thai et al., 2024). Polymeric micelles present complementary strategies by pairing hydrophobic cores for therapeutic loading with hydrophilic shells that enhance circulation and colloidal stability. Early polymer-based nanotechnologies have demonstrated robust protein-degrading effects, engaging proteasomal and autophagic clearance to inhibit tumor growth and protein aggregate formation (Lee et al., 2025). Additional micelle platforms targeting amyloid-prone proteins include curcumin-loaded NP systems that stabilize misfolded superoxide dismutase (SOD1) in amyotrophic lateral sclerosis (ALS) and short inhibitory peptides (Ac-LVFFARK-NH2) on PLGA scaffolds that suppress fibril assembly in AD (Bhatia et al., 2015; Lazar et al., 2013; Xiong et al., 2015). Similar micelles bearing tau-binding peptides have been shown to disrupt fibril growth more effectively than free peptides, highlighting the therapeutic advantage of nanoparticle-guided peptide delivery (Zhu et al., 2021).

Beyond metal- and polymer-based carriers, carbon-based nanoscaffolds and other advanced formulations also inhibit amyloidogenic processes. Hydroxylated single-walled carbon nanotubes, GO, and NP-decorated metal-organic frameworks interfere with Aβ fibrillogenesis by engaging van der Waals and electrostatic forces (Bag et al., 2016; Baweja et al., 2015; Li et al., 2014; Liu et al., 2019a; Yang et al., 2023a; Yu et al., 2012). Photodynamic nanotherapies employing BODIPY-based photosensitizers generate singlet oxygen to degrade tau aggregates, with similar strategies shown to suppress α-synuclein fibril assembly (Wu et al., 2025; Zhu et al., 2021). In type 2 diabetes models, gold nanoclusters conjugated with peptides overlapping the fibril-forming domain of human islet amyloid polypeptide (hIAPP) achieve near-complete inhibition of β-cell toxicity, whereas ultrasmall polymer-stabilized gold nanoclusters both disrupt existing fibrils and prevent the formation of new aggregates (Yang et al., 2023b; Zhou et al., 2023). Broad-spectrum suppression of amyloid aggregation has also been demonstrated using β-casein-coated iron oxide NPs, reducing fibril growth of Aβ, α-synuclein, and hIAPP by over 50% and restoring viability in zebrafish embryos (Andrikopoulos et al., 2021). Despite impressive preclinical data indicating up to 70% fibril reduction and significant neuroprotection, concerns remain regarding long-term biocompatibility, immunogenicity, and compatibility with chronic administration. Efforts are currently focused on stimulus-responsive platforms, refined ligand specificity for early misfolded intermediates, and physiologically relevant *in vitro* models, underscoring the potential of NP-based interventions for stabilizing or reversing pathological protein aggregation across diverse amyloid disorders.

Nanomaterial interventions for neuroinflammation

Nanomaterial-based strategies are increasingly recognized for their capacity to modulate neuroinflammation in diseases characterized by protein misfolding (Kinney et al., 2018). These strategies act by reprogramming microglial polarization, delivering anti-inflammatory agents, and scavenging excess ROS, thereby protecting neurons from inflammatory damage (Lu et al., 2019; Zeng et al., 2018). As resident macrophages of the CNS, microglia can promote or attenuate neuronal injury by releasing cytokines and chemokines that either amplify or mitigate inflammation. Proinflammatory M1 polarization, often mediated by NF-κB signaling, promotes the release of cytokines and chemokines that exacerbate neuronal injury, whereas M2 polarization, typically associated with STAT6 activation, supports anti-inflammatory signaling and tissue restoration (Arranz & De Strooper, 2019). Nanoplatforms designed to shift microglial phenotypes toward neuroprotective states or inhibit key inflammatory cascades offer a promising strategy to curb the neuroinflammation that accompanies protein misfolding pathologies (Table 3).

One prominent approach involves intranasal delivery to bypass the BBB and increase drug concentrations in the brain while minimizing systemic exposure (Bhuiyan et al., 2025; Dhaliwal et al., 2020; Godfrey et al., 2018; Meng et al., 2018; Rakshit et al., 2024). In a 5XFAD mouse model of AD, intranasal administration of lithium chloride (LiCl) dissolved in a Ryanodex formulation vehicle (RFV) achieved significantly

Table 2 Comparison of nanoparticle-based strategies for modulating protein aggregation and cellular processes

Approach/Method name	Nanoparticle type/Composition	Target protein/Organism	Proposed mechanism of action	References
AGXX Antimicrobial Surface Coating	Bimetallic coating	Extraintestinal *Escherichia coli* (ExPEC)	ROS generation, cell envelope damage, protein aggregation, DNA damage	Tawiah et al., 2025
Bio-templated Bimetallic Au/Ag-NPs	Bimetallic NP	Amyloid-β (Aβ) protein	Multifaceted inhibition of Aβ aggregation, esterase, and ROS	Gülseren et al., 2024
Hydroxylated Single-Walled Carbon Nanotubes	Carbon nanotube	Amyloid-β ($Aβ_{42}$)	Inhibition and disaggregation via nonpolar van der Waals interactions	Liu et al., 2019a
Metal-Chelating NPs	Chelating NP	Amyloid-β ($Aβ_{42}$), Zn^{2+} ions	Bifunctional: chelates Zn^{2+} ions and inhibits $Aβ_{42}$ fibrillation via surface interactions	Liu et al., 2017a
CuO NP-Induced Cytotoxicity in Macrophages	Copper oxide NP	RAW264.7 macrophages, SOD1	Lysosomal dissolution causes Cu-induced SOD1 misfolding and proteasomal insufficiency	Gupta et al., 2022
Curcumin NP Inhibition of SOD1 Fibrillation	Curcumin NP	Superoxide dismutase (SOD1)	Binds to amyloidogenic regions, blocking toxic species formation	Bhatia et al., 2015
Peptide-modified Gold Nanoclusters (AuNCs)	Gold nanocluster	Human islet amyloid polypeptide (hIAPP)	Enhanced hydrophobic interaction with hIAPP core in lipid membrane environment	Yang et al., 2023a
Customized Gold Nanochaperones (AuNCs)	Gold nanocluster	Amyloid-like peptides	Precise manipulation of peptide conformation via customized ligand nanointerfaces	Gao et al., 2022
Theranostic Gold Nanorods for BBB Crossing	Gold nanorod	Brain endothelium (BBB), Amyloid-β (Aβ)	Ang2 peptide facilitates BBB crossing; D1 peptide inhibits Aβ fibrillation	Palma-Florez et al., 2023
Photothermal Peptide-Functionalized Gold Nano-constructs	Gold nanoshell/nanorod	Amyloid-β (Aβ) aggregates	Photothermal absorption inhibits Aβ fibrillation	Ruff et al., 2018
Self-Assembled Bpy-BODIPY@Au Nanophotosensitizers	Gold nanourchin	Tau protein	J-aggregation enhances photostability and singlet oxygen production	Wu et al., 2025
Chiral Penicillamine-AuNPs (PGNPs)	Gold NP	Amyloid-β ($Aβ_{1-42}$)	Chirality-dependent spatial arrangement incompatible with fibrillation	Li et al., 2024b
Cationic Surfactant-Coated AuNPs (Computational)	Gold NP	α-Synuclein	Directional binding via electrostatic (C-terminus) and hydrophobic (NAC domain) interactions	Liu et al., 2023
Hybrid Peptide-Conjugated AuNPs	Gold NP	Amyloid-β ($Aβ_{42}$)	Synergistic interaction of dual-inhibitor sequence on AuNP surface inhibits oligomerization	Xiong et al., 2017
HSI/LSPR for Monitoring IAPP Aggregation with AuNPs	Gold NP	Human islet amyloid polypeptides (IAPPs)	Physical interaction with peptide; surface coating modulates immune response	Javed et al., 2019
Monolayer-Protected AuNPs (Computational)	Gold NP	Aβ(1-40) and Aβ(1-42) fibrils	Binds to the external side of fibrils via hydrophobic interactions	Tavanti et al., 2020
Proline-Functionalized AuNPs (Pro-AuNPs)	Gold NP	Hen egg white lysozyme (HEWL)	Adsorption of HEWL via hydrophobic patches blocks β-sheet formation	Karmakar et al., 2019
PVP-Conjugated AuNPs (PVP-AuNPs)	Gold NP	Hen egg white lysozyme (HEWL)	N/A	Das et al., 2017
AuNP-Decorated Porous Metal Organic Framework (MOF)	Gold NP@MOF	Amyloid-β ($Aβ_{4o}$)	Binds Aβ monomers/fibrils, suppressing fibrillation and disrupting preformed fibers	Yang et al., 2023b
Charge Density Effect on Au Surfaces (Computational)	Gold surface	Amyloid β40 (Aβ40) monomer	Adsorption of key residues prevents β-sheet formation, dependent on charge density	Kalipillai et al., 2023
Graphene Oxide Effect on Aβ Conformation (Computational)	Graphene oxide	Amyloid-β (Aβ) peptide	Inhibits α-helix to β-sheet conformational transitions upon adsorption	Baweja et al., 2015
Janus Beta Casein-Coated Iron Oxide NPs	Iron oxide NP	Aβ, α-synuclein, IAPP	Janus characteristics allow broad-spectrum inhibition of amyloid aggregation	Andrikopoulos et al., 2021
Peptide-Conjugated PLGA NPs	PLGA NP	Amyloid-β ($Aβ_{42}$)	Prevents inhibitor self-assembly, enhances Aβ interaction, redirects aggregation	Xiong et al., 2015
Core-Shell Polymer-AuNC Artificial Chaperone	Polymer-gold nanocluster	Human islet amyloid polypeptide (hIAPP)	Binds to unfolded monomers to prevent misfolding; dissolves pre-formed fibrils	Zhou et al., 2023
Tau-Targeted Polymeric Micelle Nanoinhibitor	Polymeric micelle	Tau protein	Multivalent binding inhibits aggregation, blocks seeding, and promotes degradation	Zhu et al., 2021
Dual-Inhibitor System (EGCG + Polymeric NPs)	Polymeric NP	Amyloid-β ($Aβ_{4o}$, $Aβ_{42}$)	Synergistic inhibition: NP10 blocks nucleation, EGCG suppresses elongation	Liu et al., 2017a
EGCG-Fe(iii)/PVP Coordinated NPs	Polymeric NP	Aβ40	Synergistic effect of PVP hydrophobicity and EGCG antioxidant activity	Liu et al., 2019b
Zn-doped copper sulfide quantum dots	Quantum dot	Human insulin (HI)	Electrostatic interaction with oligomers prevents self-assembly into fibers	Li et al., 2021
AGXX® Antimicrobial Silver Coating	Silver coating	Extraintestinal *Escherichia coli* (ExPEC)	ROS formation, cell envelope impairment, protein aggregation, DNA damage	Tawiah et al., 2025
Silver NP Inhibition of Aβ Oligomerization (Computational)	Silver NP	Dimeric Amyloid-β (Aβ) peptides	Alters oligomerization pathway by influencing intermolecular contacts	Thai et al., 2024
Green Synthesis Silver NPs (AgNPs)	Silver NP	α-Lactalbumin (α-LA)	Adsorption onto protein prevents aggregation-prone conformational changes	Dehvari & Ghahghaei, 2018
Green Silver NPs (B-AgNPs) as Chaperones	Silver NP	Human serum albumin (HSA)	Chaperone-like aggregation-inhibition activity	Rauf et al., 2022
Hydrophobic/Hydrophilic SPIONs	SPION	Monomeric transthyretin (mTTR)	Hydrophobic SPIONs inhibit via monomer depletion and chaperone-like oligomer adsorption	Arghavani et al., 2022
Sugar-Based NP Chaperones	Sugar-based NP	Lysozyme, insulin, Aβ, huntingtin	Stronger binding to fibril structures and enhanced cell uptake vs. molecules	Pradhan et al., 2017

Table 3 Comparison of nanoparticle-based therapeutic approaches for interventions for neuroinflammation

Approach/Method name	Nanoparticle type	Therapeutic agent	Key mechanism	References
Berberine-Bovine Serum Albumin NPs (BBR-BSA NPs)	Albumin NP	Berberine (BBR)	Improves antioxidant, proinflammatory, and amyloidogenic biomarkers	Attia et al., 2024
Celecoxib-loaded Bilosomes (CXB-BLs)	Bilosome	Celecoxib (CXB)	Inhibits neuro-inflammation by reducing Toll-like receptor (TLR4) and IL-1β levels	Darwish et al., 2024b
Hesperidin-conjugated Bimetallic NPs (Se@Au-HSP NPs)	Bimetallic NP	Hesperidin (HSP)	Reverses oxidative stress, Aβ42 levels, and up-regulation of inflammatory cytokines	Behera et al., 2023
Diosgenin-loaded Cellulose Nano-onion (DGN@CS-CNO)	Cellulose nano-onion	Diosgenin (DGN)	Inhibits protein aggregation, mitigates ROS-mediated inflammation, and induces autophagy	Zhang et al., 2026
Intranasal Cerium Oxide NPs (CONPs)	Cerium oxide NP	NP itself (antioxidant)	Exerts potent antioxidant activity, reduces inflammatory cytokines, and increases dopamine levels	Mohammad et al., 2023
Chitosan-Coated Fisetin Nanoformulation	Chitosan NP	Fisetin	Reduces oxidative stress and proinflammatory cytokines in cortex, hippocampus, and colon	Rakshit et al., 2024
ROS-Responsive TPCD NPs (TPCD NP)	Cyclodextrin NP	Tempol (ROS-responsive release)	Activates NRF2/KEAP1/HO-1 pathway to reduce oxidative stress and apoptosis	Huang et al., 2025
Immunometabolic Reprogramming Nanomodulators (GAF NPs)	Gold nanocage	Fingolimod hydrochloride	Blocks Akt/mTOR/HIF-1α to reprogram microglial metabolism and promote M2 polarization	Yang et al., 2023c
Chiral Au NPs	Gold NP	NP itself (chiral structure)	Alters gut microbiome to increase indole-3-acetic acid, ameliorating AD pathology	Guo et al., 2023
Peptide-Functionalized Lipid Nanocapsules with SPIONs	LNP	Retinoic acid (RA)	Promotes oligodendrocyte differentiation (3–5-fold) and suppresses proinflammatory cytokines (50%–70%)	Moura et al., 2023
Platelet-Hitchhiking Fucoidan-Lipid NPs (T-T3)	LNP	Triiodothyronine (T3)	Reduces infarct volume by 40%; suppresses IL-6/TNF-α; improves mitochondrial health	Syeda et al., 2025
Plasmalogen-loaded Liquid Crystalline Lipid NPs (LNPs)	LNP	Scallop-derived plasmalogens	Down-regulates Il6, Il33, Tnfa genes; improves motor function and lipid balance	Wu et al., 2024
Liposomal Dexamethasone (Lipo-Dex)	Liposome	Dexamethasone (Dex)	Reduces lesion volume, cell death, and neuroinflammation (sex-dependent effect in males)	Baudo et al., 2024
Brain-Targeted Liposomes (BTL)	Liposome	Monoclonal antibody (SynO4)	Reduces intracellular α-synuclein aggregation, decreases neuroinflammation, and improves motor function	Sela et al., 2023
Liposomal Dexamethasone (Lipo-Dex)	Liposome	Dexamethasone (Dex)	Selectively targets injured brain, reduces inflammation and cell death (sex-dependent)	Baudo et al., 2024
Microglia-Targeting Lipid NP (MG-LNP)	LNP	siRNA targeting PU.1	Reduces PU.1 transcription factor levels, leading to decreased neuroinflammation	Ralvenius et al., 2024
Macrophage-Biomimetic Nanoantidote (OT-Lipo@M)	Membrane-coated liposome	Oxytocin (OT)	Neutralizes neurotoxins and suppresses immune recognition by down-regulating TLR4 on microglia	Cheng et al., 2023
RVG29-Modified Neutrophil Membrane-Coated Nanozymes (R-NM@Fe-Ic)	Membrane-coated nanozyme	Icariside II & Fe3+ (as nanozyme)	Prevents neuronal ferroptosis, enhances mitophagy, and reduces α-synuclein aggregation	Tian et al., 2025
Apoptotic Membrane-Coated Prussian Blue NPs (apoM@mPB@Ra)	Membrane-coated NP	Rapamycin (Ra)	Promotes M2 microglial polarization, scavenges ROS, and affects mTOR signaling	Li et al., 2025
Anti-VCAM1-GM1 Micelles (Anti-VCAM1-GM1@Q)	Micelle	Quercetin (Q)	Blocks VCAM1 on cerebral vascular endothelium to reduce neuroinflammation and improve memory	Zhu et al., 2025
Cannabidiol Nanoemulsion (CBDne)	Nanoemulsion	Cannabidiol (CBD)	Normalizes oxidative stress markers and restores GSH levels in brain and duodenum	Claudino dos Santos et al., 2025
Pumpkin Seed Oil Nanoemulsion (PSO-NE)	Nanoemulsion	Pumpkin seed oil (phytoestrogens)	Increases estrogen, APP, and SYP levels; ameliorates inflammatory cascades	El-Bana et al., 2023
Brush Polymer-NAC Conjugates	Polymer	N-acetyl cysteine (NAC)	Significantly attenuates interleukin 6 (IL-6) production in activated human microglia	Mazrad et al., 2023
Microglial Scavenger Receptor-Targeting NPs (AM-NPs)	Polymeric NP	NP itself (bioactive shell)	Interrupts Aβ fibrilization and accelerates intracellular fAβ degradation in microglia	Gebril et al., 2024
Mitoapocynin-loaded Polyanhydride NPs (MPO-NP)	Polymeric NP	Mitoapocynin (MPO)	Mitigates DFP-induced reactive astrogliosis and protects neurons in the CA1 region	Meyer et al., 2023
Mitochondria-Targeted TPP/MoS2 Quantum Dots	Quantum dot	NP itself (antioxidant)	Scavenges ROS, improves mitochondrial function, and shifts microglia to anti-inflammatory phenotype	Das et al., 2023
Transferrin-Modified Mesoporous Selenium Nanoflower (Met@MSe@Tf)	Selenium NP	Metformin (Met)	Degrades Aβ deposition and increases microglial phagocytosis via enzyme-like activity	Guo et al., 2025
Transferrin-Targeted Self-Assembling NPs (SANP-TF-TEMNAP)	Self-assembling NP	TEMNAP (temazepam-naproxen hybrid)	Reduces proinflammatory markers via TSPO agonism and improves cognitive function	Casamassa et al., 2025
Agomelatine-loaded Silver NPs	Silver NP	Agomelatine	Reduces endoplasmic reticulum stress, inflammation (IL-1β, TNF-α), and apoptosis	Gelen et al., 2024
Gerbera jamesonii-loaded Solid-Lipid NPs (GJ-NPs)	SLN	*Gerbera jamesonii* extract	Modulates oxidative stress and reduces proinflammatory cytokines (TNF-α, IL-6)	Bukhari et al., 2025
Kaempferol-loaded Solid Lipid NPs (K-SLNs)	SLN	Kaempferol	Reduces infarct volume, ROS, and proinflammatory mediators (NF-κB, p-STAT3)	Ghosh et al., 2024
Antioxidant Enzyme NPs (Antioxidant NPs)	Unspecified NP	Antioxidant enzymes	Restores redox balance, shifting microglia from degenerative to regenerative phenotype	Jaffer et al., 2023
Bioengineered Yeast-Derived Vacuoles	Yeast-derived vacuole	Intrinsic hydrolytic enzymes	Reduces Aβ42 secretion and p-tau by inhibiting the NF-kB p65 signaling pathway	Nguyen et al., 2023
Luteolin/ZnO NPs (L/ZnO NPs)	Zinc oxide NP	Luteolin	Up-regulates miR-124 and protects BBB integrity by targeting C/EBPA	Moustafa et al., 2023

higher brain-to-blood lithium ratios—nearly twofold at certain time points—relative to orally administered lithium, despite lower systemic levels (Bhuiyan et al., 2025). After 12 weeks, treated mice exhibited improved cognitive function and reduced depressive behavior, accompanied by suppressed levels of IL-6 and TNF-α. Importantly, this formulation also prevented age-dependent increases in creatinine and showed no deleterious effects on thyroid function. Supporting data from Aβ1-42-challenged mice demonstrated that a chitosan-coated fisetin nanoformulation reduced cortical and hippocampal proinflammatory cytokines by 30%–40% (Rakshit et al., 2024). However, anatomical variation in nasal mucosa across species and limited long-term data remain significant obstacles for clinical translation (Bhuiyan et al., 2025).

Beyond intranasal delivery, nanocarriers designed to navigate subcellular compartments and scavenge reactive intermediates have demonstrated potential in mitigating oxidative stress and inflammation. Mitochondria-directed NPs deliver antioxidants directly to ROS-generating sites, thereby improving bioenergetics and attenuating inflammatory signaling (Ou et al., 2024; Zhang et al., 2025). In a Parkinson disease model, macrophage-derived nanovesicles conjugated with triphenylphosphonium and loaded with ursodeoxycholic acid (UDCA-NVs-TPP) increased ATP levels by 42.62% and reduced pole climb time by 48.56% (Figure 3) (Zhang et al., 2025). Comparable outcomes have been reported with echinacoside-loaded liposomes functionalized with angiopep-2, which reversed behavioral deficits by 50%–60% in MPTP-induced PD mice (Ou et al., 2024). However, maintaining serum stability while preserving mitochondrial tropism remains challenging, and small cohort sizes limit broader clinical applicability.

In parallel, selenium-based platforms have shown antioxidant and anti-inflammatory efficacy. Selenium NPs stabilized with bovine serum albumin showed a considerable reduction in lipid peroxidation, lowering nitric oxide levels to approximately 6.71 μmol/L and doubling endogenous antioxidant enzyme activity (Umapathy & Pan, 2025),

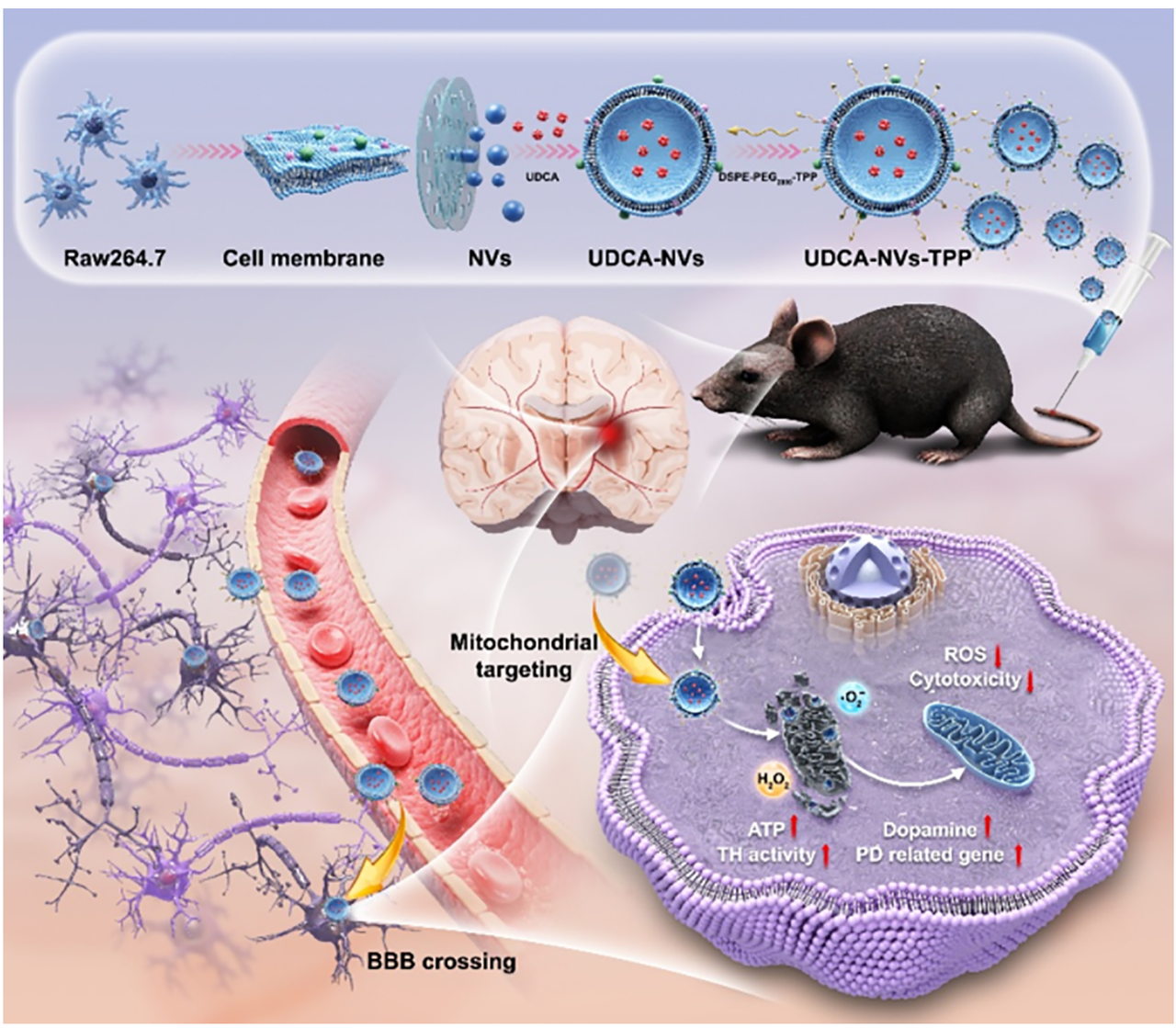

Figure 3 Schematic of mitochondria-targeted nanovesicles for ursodeoxycholic acid delivery to ameliorate neurodegeneration via restoration of mitochondrial function

Illustration outlines the design and mechanism of nanovesicles engineered to selectively accumulate in mitochondria and deliver ursodeoxycholic acid, thereby improving mitochondrial dysfunction and attenuating neurodegenerative processes. Selenium-based nanosystems exemplify how nanomaterials can confer antioxidant and anti-inflammatory effects in CNS disorders (Zhang et al., 2025).

paralleling cognitive preservation in a zebrafish model. Gold-selenium (Se@Au) bimetallic nanocomposites reduced Aβ42 accumulation and suppressed nitrite and proinflammatory cytokine production in diabetic rats. Despite these encouraging results, heterogeneity in surface coatings and doping strategies complicates cross-study comparisons, and long-term stability and safety require further evaluation (Umapathy & Pan, 2025).

Several nanomaterials also directly interfere with protein misfolding and amyloid aggregation by sequestering monomers, destabilizing oligomers, or capping fibril ends, thereby attenuating microglial overactivation. Arimoclomol-loaded nanomicelles, for instance, decreased Aβ1-42 and α-synuclein fibrillation by more than 50% and curtailed leukocyte infiltration in an acute inflammation model (Xavier-de-Britto et al., 2025). Diosgenin-loaded *Camellia sinensis*-derived cellulose nano-onions blocked 40% of early-stage protein aggregation and restored mitochondrial function in HEK293 cells. Other formulations using gold nanorods or gold-silver bimetallic NPs reported over two-thirds reduction in fibril formation, though efficacy varied with assay conditions (Gülseren et al., 2024; Liu et al., 2025). Despite these advances, most studies have relied on single-protein models that do not fully capture multifactorial disease mechanisms, and fibril inhibition measurements differ substantially across studies.

Lipid-based nanocarriers have gained attention for their immunomodulatory potential in traumatic brain injury (TBI), multiple sclerosis (MS), and AD (Baudo et al., 2024; Gebril et al., 2024; Jaffer et al., 2023). In a murine TBI model, dexamethasone-loaded liposomes administered immediately post-cortical impact reduced IL-6 and TNF-α release, decreased lesion volume, and suppressed microglial activation in male mice with TBI, although these benefits were less pronounced in females (Baudo et al., 2024). Lipid nanocapsules co-encapsulating retinoic acid and superparamagnetic NPs promoted oligodendrocyte maturation by three- to five-fold and lowered proinflammatory cytokines by 50%–70% in an MS-like demyelination model (Moura et al., 2023). However, limited circulation times and off-target sequestration highlight the need for improved stealth coatings. Furthermore, translational progress remains hindered by the complexity of scaling to large-animal models and human contexts (Baudo et al., 2024; Jaffer et al., 2023).

Concurrently, combinatorial delivery systems incorporating anti-inflammatory agents with ROS scavengers have been developed. These formulations utilize nanozymes that mimic catalase or SOD activity and often integrate immunomodulatory peptides or structural features to degrade ROS and suppress inflammatory cascades. Nanomaterials have also been used to shift microglial polarization from M1- to M2-type phenotypes by delivering ligands that enhance recognition of misfolded proteins while inhibiting proinflammatory cytokines. Strategies leveraging improved BBB transport and immune-evasive coatings enhance drug localization to affected brain regions (Chen & Liu, 2012; Drolez et al., 2016; Sun et al., 2016). For example, co-delivery of rapamycin with soluble epoxide hydrolase inhibitors has been shown to curtail glial infiltration and preserve neuronal integrity via parallel anti-inflammatory mechanisms, whereas formulations with curcumin or resveratrol harness antioxidant and inflammatory regulation to mitigate oxidative damage (Doggui et al., 2012, 2013; Lu et al., 2019). These advances reinforce the utility of platform designs that support homeostatic restoration, neuroprotection, and suppression of glial hyperactivation. Nonetheless, consistent *in vivo* targeting and long-term safety remain critical challenges.

Overall, current evidence suggests that nanomaterial-based systems can integrate precise drug delivery, ROS scavenging, and microglial reprogramming to disrupt neuroinflammatory and proteopathic cascades. Intranasal delivery achieves high CNS drug levels while minimizing systemic burdens. Mitochondria-targeted and selenium-based constructs have demonstrated potent antioxidant effects. Multiple carrier systems, including liposomes and polymers, have also shown direct inhibitory effects on amyloid and other pathogenic aggregates through monomer sequestration and fibril disruption. Nevertheless, reliable biodistribution, fibril inhibition reproducibility, and confirmation of long-term safety are ongoing challenges. Bridging these gaps will require standardized frameworks for biodistribution analysis, fibril inhibition testing, and large-animal validation that incorporate sex-specific immune variables. Parallel advances in nanomaterial design are expected to accelerate the development of targeted, durable neuroprotective therapies for chronic neurodegenerative conditions.

NEW TARGETING STRATEGIES AND SMART RESPONSIVE DESIGN

Recent advances have enabled the development of nanoplatforms engineered to detect pathological biochemical cues in the brain, including elevated protease activity, acidic pH, and excessive ROS. These platforms integrate stimulus-responsive features that trigger drug release or catalytic activation specifically within diseased microenvironments. Such precision confines therapeutic action to affected sites, thereby minimizing systemic exposure and off-target effects. This localized approach is particularly valuable for tackling protein misfolding and neuroinflammatory processes, where sparing unaffected tissue is essential. Intelligent nanoplatforms co-delivering pathologically responsive agents and immunomodulatory components offer a promising solution for simultaneously targeting misfolded proteins and restoring immune equilibrium.

Certain nanoconstructs are engineered with coatings or ligands that selectively bind misfolded protein species, facilitating their destabilization and clearance. These systems often include anti-inflammatory agents that suppress harmful cytokine release or guide activated microglia toward less destructive states. To ensure spatial specificity, NPs can be designed to activate only in the presence of elevated protease activity or high oxidative stress, thereby minimizing effects on healthy tissue while targeting pathogenic aggregates. An additional strategy involves using cleavable linkers or surface moieties—such as boronic esters or disulfide bonds—that remain stable under normal physiological conditions but degrade in response to high ROS or low pH. This enables the controlled release of small-molecule inhibitors of amyloidogenic peptides or catalytic agents that disassemble aggregates at the site of pathology, limiting off-target toxicity. When combined with surface modifications that enhance BBB penetration and lesion-specific accumulation, these dual-targeting platforms enable selective therapeutic action within neuroinflammatory and proteinopathy-associated brain regions.

Coordinating anti-aggregation therapies with

immunomodulation enables engagement of innate clearance pathways. Certain platforms incorporate short peptide motifs such as KLVFF, which selectively bind misfolded proteins and facilitate their sequestration into degradable nanostructures (Du et al., 2018). In parallel, co-delivered immunomodulatory peptides or siRNA can be activated *in situ* to suppress overproduction of proinflammatory cytokines. Similarly, multifunctional NP cores, including CeO_2, can continuously scavenge ROS and release additional agents under high oxidative loads (Singh et al., 2011). When functionalized with aggregation-targeting ligands, these constructs accumulate in diseased regions, neutralize redox imbalance, and respond to inflammatory signals by disassembling their outer shell to enable localized drug release.

Engineered cell membranes offer an additional avenue for advanced nanoplatform design by leveraging receptors attuned to local inflammatory signals. Membrane-coated or hybrid NPs equipped with inflammation-responsive receptors preferentially accumulate at lesion sites, where they release immunomodulatory compounds or aggregation-disrupting agents (Agyare et al., 2008; Cassidy et al., 2020; Saeedi et al., 2019). Local pathophysiological signals—such as excess protease activity, acidic niches, or bursts of reactive oxygen species—trigger the shedding of protective coatings, thereby activating the therapeutic agents specifically within pathological regions. This design confines drug activity to disease-relevant environments, enabling localized remodeling of protein aggregates and attenuation of neuroinflammation, while minimizing systemic exposure and off-target effects. By incorporating protease- or oxidant-responsive elements into the carrier composition, selectivity and safety are further enhanced, reducing the risk of unintended immune activation and inflammatory cascades.

Smart responsive biomaterials

Smart nanomaterials that respond to pathological cues in the brain offer a promising strategy for selectively targeting regions burdened by misfolded proteins and chronic inflammation. By designing platforms that respond to localized acidity, redox imbalance, or disease-specific enzymatic activity, therapeutic release and targeting can be precisely confined to affected sites. These adaptive systems improve drug efficacy in neurodegenerative disorders such as Alzheimer's disease by concentrating bioactive agents at pathological loci while minimizing off-target distribution. Current strategies include tailoring nanocarriers to selectively respond to the molecular hallmarks of degenerating tissue, thereby synchronizing delivery with the presence of protein aggregates or neuroinflammation.

Key metabolic features of AD—such as elevated ROS and acidic microenvironments—provide potent triggers for these systems. Redox-sensitive linkers, including arylboronic esters, degrade in the presence of excess ROS and can be integrated into gold nanocages, polymeric carriers, or liposomes, ensuring carrier stability in healthy tissue while enabling selective degradation in inflamed or oxidatively stressed regions. Acid-labile bonds or pH-responsive polymers similarly enable controlled cargo delivery in glial activation zones or inflamed tissue, remaining stable at physiological pH. These targeting strategies are often enhanced with ligands that recognize disease markers, such as KLVFF motifs for Aβ or CCR2-, transferrin-, and RAGE-binding sequences that exploit receptor up-regulation in AD pathology. The combination of biochemical responsiveness and receptor-guided targeting ensures that nanocarriers accumulate at pathogenic sites and triggers payload release in response to ROS or altered pH. Parallel strategies involve polymeric carriers or liposomes that shed their outer shells in response to inflammation, delivering immunomodulatory agents directly into sites of persistent neuroinflammation (Fan et al., 2018; Lazar et al., 2013; Li et al., 2016).

A wide range of nanomaterials, including polymeric, carbon-based, lipid-based, and metal-containing systems, have been explored for modulating protein misfolding and neuroinflammation in AD and related neurodegenerative disorders (Hatami et al., 2023; Jin et al., 2021; Song et al., 2014). Polymeric NPs like PLGA carriers can inhibit aggregation processes *in vitro*, with efficacy influenced by NP concentration and temperature shifts (Paul et al., 2025; Xavier-de-Britto et al., 2025). Conjugating trehalose or similar molecules to polymeric particles further enhances aggregation-inhibiting potential, enabling effective treatment at reduced doses (Debnath et al., 2017; Mandal et al., 2023). Carbon dot-based systems functionalized with Aβ-binding moieties provide fluorescence-based diagnostic cues while preventing pathological fibril formation (Li et al., 2023). Lipid-based or micellar nanocarriers, such as transferrin-functionalized mesoporous selenium or phytosterol-liposome constructs, similarly enhance BBB penetration, reduce Aβ deposition, and deliver anti-inflammatory cargo over extended periods (Cai et al., 2020; Chen et al., 2024; Guo et al., 2025; Spuch & Navarro, 2011). Metal and bimetallic NPs provide catalytic or redox-based interactions that interfere with misfolded proteins. For instance, AuNPs functionalized with photosensitizers generate singlet oxygen to disrupt tau fibrils (Wei et al., 2024), while CeO_2 NPs have been shown to bind α-synuclein aggregation motifs and restore aggregation to near-baseline levels (Pérez Gutiérrez et al., 2024; Yao et al., 2024). Bimetallic Au/Ag nanohybrids reduce Aβ aggregation and suppress ROS generation (Gülseren et al., 2024), while inorganic-organic hybrids incorporate metal cores with polymeric or polyphenolic coatings to achieve near-complete inhibition of α-synuclein and Aβ fibrils (Andrikopoulos et al., 2021; Guo et al., 2024; Liao et al., 2012). The lipophilic or amphiphilic nature of these carriers supports high drug-loading capacity and efficient CNS penetration, facilitating targeted treatment while limiting systemic toxicities (Rinaldi et al., 2018; Spuch & Navarro, 2011). Strategic design elements, including surface charge and ligand specificity, also mitigate unintended NP-protein interactions and ensure selective engagement with disease-relevant targets (Liu et al., 2023; Yao et al., 2024).

Analogous strategies have been applied to other protein misfolding disorders, including ALS and prion diseases. In ALS models, advanced nanocarriers have been used to deliver antisense oligonucleotides targeting SOD1, with calcium phosphate-lipid NPs combined with focused ultrasound enabling BBB penetration and significantly reducing motor neuron loss (Ediriweera et al., 2025). Parallel approaches targeting lysosomal ion channels implicated in disease progression have been shown to prolong neuromuscular function in $SOD1^{G93A}$ mice (Tedeschi et al., 2024). In prion disorders, NP-based diagnostic platforms such as (Nano-QuIC) improve diagnostic sensitivity by a factor of ten and shorten turnaround times without increasing false positives (Christenson et al., 2023). Proteomic and spectroscopic studies have demonstrated widespread

perturbation of proteostasis networks in these disorders, underscoring the need for multifactorial therapeutic strategies (Son et al., 2024; Zhu et al., 2024). Chiroptical and plasmonic sensors enable detection of fibrillar species at nanomolar levels in patient-derived samples (Kumar et al., 2018), while recent studies on cerebrovascular impairment in AD indicate that early structural deterioration may precede overt amyloid pathology (Li et al., 2024d; Wang et al., 2023b). Collectively, these findings support the application of "smart" biomaterials for early detection and targeted intervention in neurodegenerative diseases. By harnessing disease-specific cues such as oxidative stress, altered pH, glial overactivation, and aberrant protein conformations, nanocarriers achieve site-specific drug delivery, minimize systemic toxicity, and enhance therapeutic precision. Continued research into NP-protein interfaces will help advance the rational design of customized nanomedicines that interrupt pathogenic cascades and improve clinical outcomes.

High-performance nanoprobes for diagnostics

Recent advances in nanoprobe engineering have enabled earlier and more precise detection of pathological protein misfolding and neuroinflammatory lesions characteristic of neurodegenerative diseases (Table 4). By exploiting tunable optical, magnetic, and photothermal properties, these nanosystems can achieve targeted recognition of Aβ fibrils, hyperphosphorylated tau, and activated glial regions that disrupt neuronal function (Gao et al., 2020b). Their high-contrast performance supports real-time, noninvasive monitoring of disease progression and therapeutic response. Metal oxide NPs conjugated with Aβ- or tau-specific antibodies facilitate sensitive signal generation through mass spectrometry or fluorescence-based readouts (Moon et al., 2020). Functionalization with polyethylene glycol targeting ligands further reduces nonspecific adsorption, prolongs circulation time, and enhances detection accuracy.

Ultrasmall superparamagnetic iron oxide (SPIO) NPs provide enhanced magnetic resonance imaging (MRI) contrast for early AD detection (Cheng et al., 2015b). When conjugated with NIR dyes, these iron oxide cores integrate magnetic and optical channels to localize Aβ deposits at high resolution while also detecting neuroinflammatory lesions (Gao et al., 2020a; Hu et al., 2015). Quantum dots, known for strong emission profiles and photostability, provide distinctive wavelength tuning for deeper tissue penetration. Functionalization with anti-Aβ antibodies enables these dots to distinguish assembly states across live animal models and clarify disease progression and therapy responses (Feng et al., 2013). NIR photothermal probes, including gold nanorods and black phosphorus nanosheets, serve as dual-function reporters, confirming binding to pathological targets

Table 4 Smart responsive biomaterials targeting misfolded protein aggregates and neuroinflammatory regions

Approach/Method name	Biomaterial composition	Key mechanism	References
Ferromagnetic Substrate-Mediated Assembly	Ferromagnetic substrates	Modulation of fibril formation dynamics via substrate spin polarization (CISS effect)	Kapon et al., 2025
Biomimetic Nanozymes (R-NM@Fe-Ic)	Neutrophil membrane-coated Fe-Icariside II nanozymes	Iron chelation, antioxidant activity, mitophagy promotion, targeted BBB crossing	Tian et al., 2025
Dual-Target Carbon Dots (Ce CDs)	Cerium-doped carbon dots	Aβ aggregation inhibition via electrostatic interaction, ROS scavenging	Wang et al., 2025c
Functionalized Carbon Dots (CDs@TGM-IL)	Guanidine salt ionic liquid-functionalized carbon dots	Inhibition of Aβ aggregation, disaggregation of mature fibrils, ROS scavenging, BBB crossing	Wang et al., 2025d
PLGA NP Therapy	Poly(D,L-lactide-co-glycolic) acid (PLGA) NPs	Inhibition of temperature-dependent tau aggregation and disassembly of preformed aggregates	Paul et al., 2025
FUS-Enhanced NP Delivery	Calcium phosphate lipid NPs with SOD1 antisense oligonucleotides	Focused ultrasound-mediated BBB opening for enhanced systemic antisense oligonucleotide delivery	Ediriweera et al., 2025
Lysosomal Channel Stabilization	Self-assembling lipid formulation of PI(3,5)P2	Stabilization of TRPML1 lysosomal channel activity to regulate autophagy	Tedeschi et al., 2024
Drug-Loaded Selenium Nanoflowers	Transferrin-modified mesoporous selenium carrying metformin	Receptor-mediated BBB transport, pH-responsive drug release, Aβ degradation, neuroinflammation relief	Guo et al., 2025
Core-Shell Nano-Photosensitizers	AuNPs with azobenzene-spiropyran core-shell	Enhanced singlet oxygen generation (phototherapy), inhibition of tau aggregation, dendritic growth promotion	Wei et al., 2024
Iridoid-Cerium Nanocomposite (GH/CeO2 NPs)	Geniposide & harpagoside-loaded CeO2 NPs	Inhibition of Aβ/Tau aggregation, inhibition of AChE/BuChE activity, antioxidant properties	Pérez Gutiérrez et al., 2024
Antifibrillar Cerium NPs	Cerium oxide NPs (CeO2 NPs)	Inhibition of α-synuclein fibrillation via active site interaction, antioxidant activity	Yao et al., 2024
All-in-One Theranostic CDs	Congo red-derived carbon dots (CA-CDs)	Turn-on fluorescence imaging of aggregates, inhibition of aggregation, ROS scavenging	Li et al., 2023
Plasmonic Chiral Sensing	Gold nanorods	Specific fibril detection via induced helical arrangement and chiroptical signals	Kumar et al., 2018
Chiral SERS Nanosensing	Chiral Pt@Au triangular nanorings	Ultrasensitive label-free SERS detection of Aβ (LOD: 4×10^{-15} M for fibrils)	Wang et al., 2021
Selenium NP Therapy (Nano-Se)	Selenium NPs	Reduction of oxidative stress, inhibition of huntingtin aggregation, down-regulation of histone deacetylases	Cong et al., 2019
NIR-Propelled Nanomotors (JNM-I)	Inhibitor-conjugated Janus nanomotors	NIR-driven motion (self-thermophoresis) to enhance modulation of Aβ aggregation & BBB crossing	Liu et al., 2020b
Tau-Targeted Nanoinhibitors	Tau-binding peptide decorated polymeric micelles	Inhibition of tau aggregation & cellular seeding, promotion of aggregate degradation	Zhu et al., 2021
Lysosomal Re-acidification (aNPs)	Acidic NPs	Lysosomal re-acidification to enhance lysosomal activity and α-synuclein degradation	Arotcarena et al., 2022
Dual-Action Antioxidant NPs	Ferulic acid diacid & tannic acid NPs	Inhibition of α-synuclein fibrillization and suppression of proinflammatory microglial activation	Zhao et al., 2020
Biodegradable Multifunctional NPs	Catechin-loaded, trehalose/dopamine-terminated polylactide NPs	Inhibition of polyQ aggregation, reduction of oxidative stress, enhanced cell proliferation	Mandal et al., 2020

via thermal output and fluorescence (Yin et al., 2016).

Carbon-based quantum dots, with intrinsic fluorescence and BBB permeability, exhibit strong binding to aggregated proteins and can be tailored for selective imaging of diseased tissues (Feng et al., 2013; Liu et al., 2015; Wang et al., 2018b). Incorporation of oligomer-targeting peptides enables detection of early oligomers, considered more neurotoxic than mature fibrils (Haass & Selkoe, 2007; Plissonneau et al., 2016; Xu et al., 2022). Multifunctional nanomaterials combining fluorescence and MRI, such as metal-organic frameworks with iron oxide cores and Aβ-targeting peptides, amplify magnetic signals while allowing concurrent optical tracking of neuronal lesions. Activatable probes responsive to local oxidative stress or other pathophysiological triggers can turn on fluorescence, alter relaxivity, or enhance photothermal output specifically within affected regions, providing precision diagnostics at preclinical and clinical stages.

Crossing the BBB remains a critical challenge for NP-based diagnostics (Pardridge, 2012). Targeting ligands against transferrin or chemokine receptors, coupled with precise control of NP charge, size, and hydrophilicity, markedly improves brain uptake at sites of misfolded proteins or inflammation. Stealth coatings extend circulation and promote focal accumulation, as demonstrated by B6 peptide-conjugated, sialic-acid-modified selenium NPs, lactoferrin-coated lipid carriers, and intranasal chitosan-based formulations. These approaches enhance diagnostic accuracy for AD and PD and offer parallel opportunities for therapeutic delivery via encapsulation or conjugation of disease-modifying molecules. Accumulating evidence further indicates that NPs can directly modulate pathological protein aggregation and mitigate toxic species formation.

Certain formulations have been shown to influence aggregation dynamics. Curcumin- and polyphenol-loaded nanocarriers can suppress SOD1 fibrillation in familial ALS, while GO derivatives disrupt β-sheet formation in Aβ. In PD models, bare Fe_3O_4 variants have been shown to accelerate α-synuclein oligomerization, whereas lysine-coated NPs suppress aggregate formation and reduce cytotoxicity. Stable nucleic acid lipid particles can deliver siRNAs across the BBB to silence pathogenic genes such as ataxin-3 in Machado-Joseph disease, thereby ameliorating neurodegeneration and improving motor performance. These findings underscore the capacity of surface-engineered carriers to redirect misfolding pathways toward non-toxic intermediates.

Simultaneously, next-generation sensing platforms, including mesoporous silica NPs and conductive nanocomposites, enable detection of ROS and metal-ion dysregulation associated with neuroinflammation. NP-enhanced imaging mass spectrometry has revealed lipid perturbations in alcohol-related neuroinflammation and may be extended to other pathologies. Magnetic NP probes remain pivotal, with sub-100 nm superparamagnetic iron oxide particles functionalized with curcumin or Congo red, penetrating *in vitro* BBB models and providing strong MRI contrast for Aβ plaque detection (Cheng et al., 2015a; Hu et al., 2015). Manganese oxide NPs, which release Mn^{2+} *in situ*, allow dynamic switching between T2- and T1-weighted imaging, increasing diagnostic sensitivity in dopaminergic regions relevant to PD (McDonagh et al., 2016). Tuning NP composition and surface chemistry enhances imaging stability while minimizing immunogenic risks.

Beyond magnetic approaches, optical and electrochemical strategies offer complementary detection modalities. Lanthanide-doped upconversion NPs responsive to Zn^{2+} enable real-time tracking of metal-ion dysregulation in AD models (Peng et al., 2015), while surface-enhanced Raman scattering (SERS) probes functionalized with Al^{3+}-MBA complexes or peptide-dye conjugates differentiate oligomeric from fibrillar protein aggregates based on distinct spectral and fluorescence signatures (Guerrini et al., 2015; Pradhan et al., 2015). AuNPs support localized surface plasmon resonance (LSPR) assays that detect Aβ and α-synuclein at nanomolar concentrations through plasmon band red-shifts (Cheng et al., 2015a; Kang et al., 2015; Kim et al., 2018). Quantum dot-based sensors provide subcellular resolution for tyrosinase imaging in PD (Zhu et al., 2015). Although challenges such as NP instability and biological interference persist, these techniques consistently demonstrate robust specificity and high signal-to-noise ratios.

Collectively, diagnostic nanoprobes based on iron and manganese oxides, gold nanostructures, quantum dots, carbon dots, and polymeric matrices enhance the detection of protein misfolding and neuroinflammation in neurodegenerative models. Integration of optical, magnetic, electrochemical, and photothermal modalities supports high-resolution localization of pathogenic assemblies and facilitates combined diagnostic and therapeutic applications. While long-term biocompatibility, immune activation, and cross-species variability remain to be fully addressed, advances in NP engineering and surface modification hold considerable promise for clinical translation. Early and sensitive profiling of pathological changes may enable targeted, patient-specific management of AD, PD, ALS, and related conditions, linking precision diagnostics to effective disease-modifying interventions.

Artificially regulated nanozymes

Bioinspired nanozymes that mimic antioxidant enzymes such as catalase and SOD have emerged as promising candidates for mitigating oxidative stress and neuroinflammation—two key drivers of neurodegenerative disorders including AD and PD (Table 5). Excessive production of ROS, often exacerbated by misfolded proteins, leads to neuronal damage and chronic glial activation (Jampilek, 2019). Engineered nanozymes that replicate endogenous enzyme activity restore redox homeostasis and attenuate inflammatory cascades that promote neuronal injury, especially when targeted to subcellular regions with high oxidative burden. These targeted systems can interrupt early-stage protein aggregation and suppress prolonged inflammatory signaling, prompting growing interest in nanozymes as integrated tools to address oxidative stress, aberrant protein assembly, and neuroimmune dysregulation.

CeO_2 and MnO_2 nanozymes are among the most extensively studied platforms, exhibiting dual antioxidant and anti-inflammatory benefits. CeO_2-based constructs harness reversible cycling between Ce^{3+} and Ce^{4+} states to mimic SOD activity (Singh et al., 2011) and reduce oxidative injury, particularly when conjugated with mitochondrial-targeting ligands such as triphenylphosphonium. MnO_2-based nanozymes scavenge ROS through redox conversion of superoxide radicals and hydrogen peroxide, complementing therapies that disrupt amyloid fibrils or inhibit tau phosphorylation. These nanozymes also modulate microglial polarization toward anti-inflammatory phenotypes that

Table 5 Artificially regulated nanozymes mitigating oxidative stress and neuroinflammation

Approach/Method name	Core nanomaterial	Regulation/Activation method	Primary therapeutic mechanism	References
mPDA-SeMn-IR Nanosystem	Mesoporous polydopamine with SePh, MnO_2, IR-1048	NIR-II laser irradiation	Wireless deep brain stimulation via Ca2+ signaling; ROS elimination	Zhou et al., 2025b
Sono-Piezocatalytic Nanorods	Piezoelectric barium titanate nanorods	Ultrasound	ROS generation for oxidative degradation of amyloid fibrils	Das et al., 2025
Engineered Hybrid Exosomes (RPDA@Rb-A)	Polydopamine NPs with resveratrol and hybrid exosome membrane	Near-infrared laser irradiation	Photothermal Aβ degradation; Drug delivery; Microglia modulation	Du et al., 2025
Macrophage Membrane-Coated Prussian Blue (PB NPs/MM)	Prussian blue NPs with macrophage membrane coating	Near-infrared laser irradiation	Cu2+ chelation; ROS reduction; Photothermal Aβ ablation	Li et al., 2025
Sonosensitizer-Loaded Polymer Micelles	Polymer micelle with chlorin e6 or protoporphyrin IX	Ultrasound	Singlet oxygen generation inducing autophagic flux	Sarkar et al., 2024
Photocatalytic Gold Nanocluster Assay (DTT@BSA-AuNCs)	DTT-assisted BSA-stabilized gold nanoclusters	LED irradiation	Fluorescence-based antioxidant detection via singlet oxygen generation	Swain et al., 2024
Neutrophil Membrane-Coated MOF Nanozyme (Neu-MOF/Fla)	Metal-organic framework with neutrophil membrane coating	Photo-triggering	Hydrolytic Aβ degradation; Anti-inflammatory CO release; Microglia modulation	Liu et al., 2024a
HOF-based Sonosensitizer (USI-MHOF)	Hydrogen-bonded organic framework (HOF) from Mn-TCPP	Ultrasound	Singlet oxygen generation for Aβ oxidation; CAT/SOD-like activity	Ya et al., 2024
Biomimetic Upconversion Nanobait (UCNP/Cur@EM)	Upconversion NPs with curcumin and erythrocyte membrane	Near-infrared (NIR) irradiation	Photodynamic therapy (ROS generation) for Aβ degradation; Aβ trapping	Wang et al., 2024b
Colloidal Au Nanocrystals (CNM-Au8)	Surfactant-free gold nanocrystals	Photoexcitation-modulated catalytic activity	Catalytic NADH to NAD+ conversion for bioenergy production	Wang et al., 2024c
Peptide-Modified Prussian Blue NPs (PBK NPs)	Peptide-modified Prussian blue NPs	Near-infrared (NIR) irradiation	Multi-enzyme antioxidant activity; Photothermal Aβ disaggregation	Song et al., 2023

enhance phagocytosis of misfolded proteins (Lu et al., 2019; Ren et al., 2020; Zeng et al., 2018).

Prussian blue (PB) analogs exemplify multifunctional nanozymes with catalase- and SOD-like activities that suppress both ROS and protein aggregation. For example, PB-based formulations reduced pathological protein accumulation and neuroinflammation in models of AD and PD (Figure 4) (Li et al., 2025; Liu et al., 2024a; Ma et al., 2025a; Ramgopal et al., 2025; Song et al., 2023), while neutrophil membrane-coated cerium-doped Prussian blue NPs (NM@PB-Ce, ~142 nm in diameter) exhibited catalytic degradation of ROS and suppression of inflammasome activation in neuronal cultures (Ma et al., 2025b). Macrophage membrane-functionalized PB constructs are also reported to enhance metal chelation and disrupt amyloid fibrils via photothermal effects, thereby lowering proinflammatory microglial markers (Li et al., 2025). Advanced designs, including etched CoFe PB analogs, offer higher catalytic efficiency than natural horseradish peroxidase, enabling submicromolar detection of hydrogen peroxide (Ramgopal et al., 2025). These nanozymes have shown cognitive and motor benefits in rodent models; however, concerns about metal-ion release and long-term safety highlight the need for extended biocompatibility assessments before clinical translation.

Metal-organic framework (MOF) nanozymes provide another adaptable platform for modulating ROS and protein aggregation through the rational selection of metal nodes and organic linkers that confer antioxidant or proteolytic-like activity. For example, cerium dioxide nanoclusters have been integrated into a CRISPR activation construct (CMOPKP) for application in 3xTg-AD mice, restoring redox balance, inhibiting oxidative pathways, improving exploratory behavior, and reducing plaque load (Yang et al., 2024). The application of Zr-FeP MOF@Man liposomes has also been shown to lower neuroinflammatory markers by over 30% in PD models compared to free-drug controls (Li et al., 2024d). However, post-synthetic modifications and size variation can alter catalytic output and biodistribution, complicating clinical translation despite promising efficacy in BBB permeability. Transition metal-based nanozymes have garnered attention due to their ability to adjust redox behavior mimicking antioxidant or proteolytic enzymes. Notably, Co-Cu dual-atom catalysts have been shown to induce superior decomposition of hydrogen peroxide than single-metal analogs (Wang et al., 2025a) and to alleviate ROS burden and α-synuclein aggregation in *Caenorhabditis elegans* PD models. Similarly, Fe-isolated single-atom nanozymes reduce α-synuclein levels and improve motor coordination in murine PD models (Liu et al., 2024b). Furthermore, Cu_2-xSe nanozymes enhance microglial Aβ phagocytosis in AD models (Wang et al., 2025b), while CeO_2-based variants have been found to decrease superoxide by over 70% to block proinflammatory cytokines (Gao et al., 2024). Although doping and gating strategies enable atomic-level control, subtle shifts in redox potential require optimization to preserve catalytic efficiency and *in vivo* stability.

Metal and carbon nanoclusters further extend nanozyme utility through tunable enzyme-like activities sensitive to intracellular triggers. For example, DTT@BSA-AuNCs achieved 0.08 μmol/L detection limits for antioxidants and selectively quenched ROS in human saliva, while platinum nanozymes (5 nm in size) reduced ROS by 50%–70% in neurovascular cell lines (Swain et al., 2024; Tarricone et al., 2023). Graphene quantum dots derived from coal waste matched 1 U/mL of native SOD activity, while gold nanocrystals promoted NADH oxidation to NAD^+, rescuing 80% of cells from apoptosis (Das et al., 2023; Wang et al., 2024b). Although precise control of size and surface chemistry improves biocompatibility, heterogeneous protein corona formation across tissues remains a key obstacle to reproducible therapeutic outcomes. These nanozyme strategies collectively integrate redox regulation and anti-aggregative functions, offering a multifaceted therapeutic

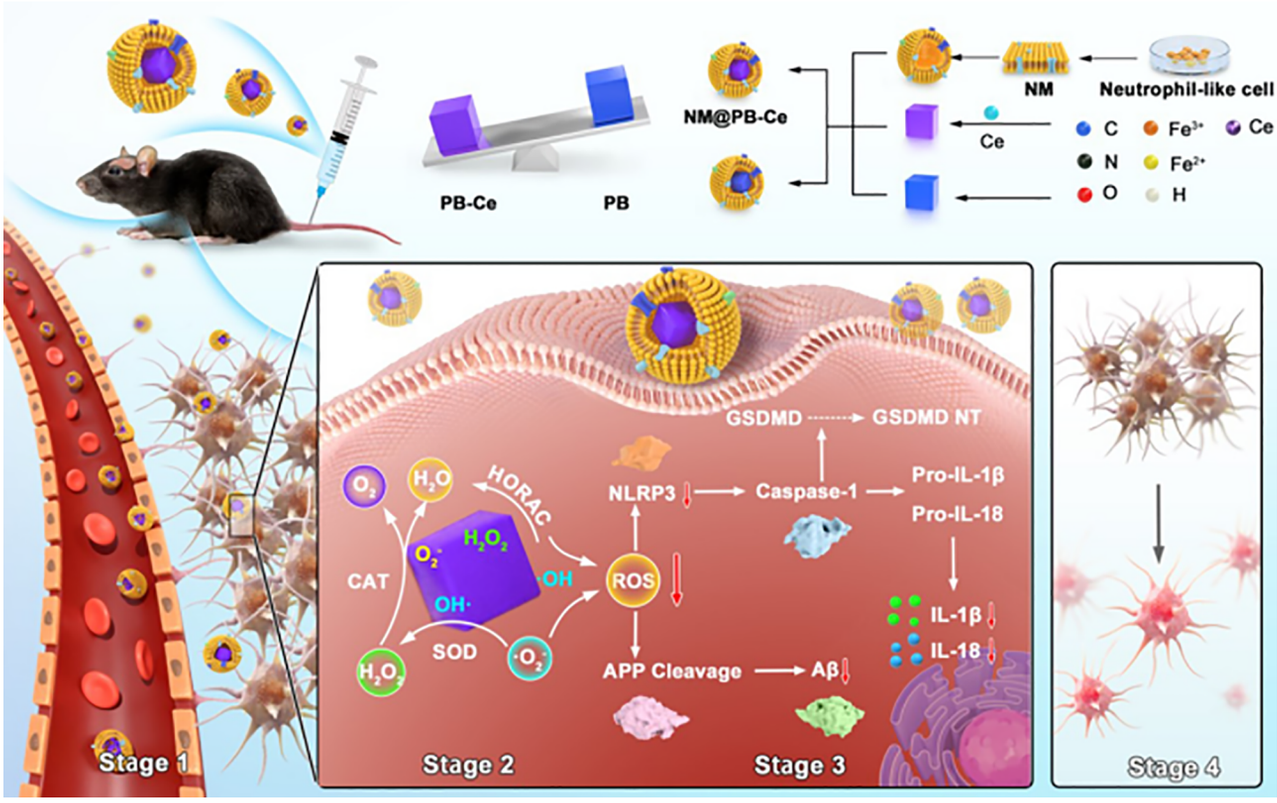

Figure 4 NM@PB-Ce nanozymes effectively cross the BBB to target AD-affected regions with robust enzymatic activity

The NM@PB-Ce nanozyme traverses the BBB and accumulates in affected brain regions, where it exhibits potent catalytic activity. In AD mouse models, this platform reduces oxidative stress, suppresses inflammation, and attenuates both tau phosphorylation and Aβ aggregation. These effects correlate with improved motor function and memory performance. The findings support the therapeutic potential of NM@PB-Ce for treating inflammation-linked neurodegenerative disorders (Ma et al., 2025a).

platform for AD, PD, and related conditions. Prussian blue variants and MOFs enable targeted delivery and high catalytic versatility, while transition metal-based systems feature adjustable atomic-level sites that can optimize redox reactions. Despite persistent challenges in catalytic efficiency, mass production, and long-term biocompatibility, continued advancements in rational design and improved pharmacokinetic understanding suggest that catalytic nanoplatforms hold significant potential for transforming neurodegenerative disease therapy.

INTEGRATIVE THERANOSTIC PARADIGM

Lipid-based nanocarriers have gained prominence as versatile platforms for delivering therapeutic and protective payloads across biological barriers to mitigate neuroinflammation and protein misfolding (Elnaggar et al., 2015; Fan et al., 2018; Haney et al., 2015; Lazar et al., 2013; Li et al., 2016; Mancini et al., 2016; Sachdeva et al., 2015; Turjeman et al., 2015). Their biocompatibility and capacity to encapsulate antioxidants or drugs enable efficient targeting of neural tissues. Nanoscale exosomes (~100–200 nm) have been shown to enhance neuronal uptake and enzymatic activity of intranasally delivered catalase, mitigating behavioral deficits in PD mouse models (Haney et al., 2015). Cubosomes and SLNs also leverage lipid-mediated delivery to improve bioavailability and therapeutic effects. For instance, application of Tween-modified monoolein cubosomes (T-cubs) (~167 nm, 87% entrapment efficiency) increased oral absorption of piperine in an AD model, reducing inflammation and modulating cholinergic signaling (Elnaggar et al., 2015), while SLNs loaded with sesamol reduced oxidative stress and serum TNF-α levels, improving cognitive performance (Sachdeva et al., 2015). Liposomal platforms, including sterically stabilized formulations, have reduced clinical symptoms and pathological lesions in MS (Turjeman et al., 2015), while liposomes functionalized with phosphatidic acid and an apolipoprotein E-derived peptide increased plasma Aβ levels through a “sink effect” in AD (Mancini et al., 2016). Despite their promise in crossing the BBB, factors such as variable intranasal absorption, rapid clearance by the reticuloendothelial system, and methodological inconsistencies across studies hinder direct comparison of outcomes. Nonetheless, consistent evidence affirms the ability of lipid-based nanocarriers to deliver antioxidant, anti-amyloid, and anti-inflammatory agents to the brain with demonstrable therapeutic effects (Cai et al., 2020; Elnaggar et al., 2015; Haney et al., 2015; Mancini et al., 2016; Sachdeva et al., 2015; Turjeman et al., 2015; Zhou et al., 2020). Continued refinement of formulations, dosing regimens, and administration routes remains critical for advancing clinical translation.

Polymeric, dendrimeric, and protein-based nanocarriers offer multifunctional platforms for neuroprotection and anti-aggregation. For example, chitosan NPs (CS-NPs) (~200–300 nm, 80%–82% entrapment efficiency) enhanced cognitive performance in Wistar rats when intranasally administered with piperine, enabling a nearly 20-fold reduction in the required oral dose while conferring anti-inflammatory and anti-apoptotic benefits in AD models (Carpentieri et al., 2012;

Elnaggar et al., 2015; Wu et al., 2016). Similarly, PLGA NPs conjugated with an inhibitory peptide effectively suppressed Aβ fibrillogenesis at 20 μg/mL, outperforming the free peptide at equivalent concentrations (Xiong et al., 2015). Dendrimers, characterized by high densities of functional groups for binding toxic oligomers, disrupted prion protein inclusion bodies and decreased amyloidogenicity in Thioflavin T assays via pH-independent cationic pyridylphenylene structures (Sorokina et al., 2016). Cationized albumin conjugated with a metal chelator has been shown to mitigate Aβ-induced deficits in murine models (Kamalinia et al., 2015). SPIO NPs further expand functionality by enabling MRI. For example, DNA-hybridized SPIO NPs labeled neural stem cells at concentrations up to 50 μg/mL without toxicity, permitting MRI detection for one month post-transplantation (Egawa et al., 2015). Application of a 0.6 T magnetic field improved homing of SPIO-labeled neuroprogenitor cells in a TBI model (Shen et al., 2016). Labeling protocols, including double-stranded DNA functionalization versus electrostatic adsorption, modulate intracellular stress responses and paramagnetic fidelity. Overall, these platforms enhance therapeutic stability while enabling concurrent neuroimaging.

Inorganic and carbon-based nanomaterials also demonstrate capacity to suppress aggregation and neuroinflammation. For instance, in bEnd.3 and PC12 cells, selenium NPs modified with sialic acid and a targeting peptide (B6-SA-SeNPs) improved BBB permeability *in vitro*, disassembled Aβ fibrils into less cytotoxic forms, and reduced cell death (Sun et al., 2019; Yin et al., 2015). AuNPs conjugated with polyoxometalates or Aβ-binding peptides nearly eliminated fibril formation at micromolar doses, although variations in synthetic routes and surface chemistry affected biocompatibility (Araya et al., 2008; Gao et al., 2015; Kogan et al., 2006; Liao et al., 2012). Graphene quantum dots, measuring only a few nanometers, suppressed Aβ aggregation while exhibiting minimal cytotoxicity and likely BBB permeability (Liu et al., 2015). GO exploited π–π interactions with aromatic residues in Aβ, and partially reduced GO stabilized α-helical segments to prevent β-sheet transitions (Baweja et al., 2015; Yang et al., 2015). However, silica NPs of 50–60 nm triggered aberrant protein aggregation in *Caenorhabditis elegans*, particularly in the presence of compromised proteostatic mechanisms (Scharf et al., 2016). In contrast, europium hydroxide nanorods ($Eu(III)(OH)_3$) promoted autophagic clearance of mutant huntingtin aggregates without activating the AKT-mTOR pathway, illustrating how distinct cell signaling processes can mitigate accumulation (Wei et al., 2015). Particle size, surface functionalization, oxidation state, and hydrophilicity all influence BBB penetration and intracellular trafficking, necessitating systematic *in vivo* comparisons for refined safety and efficacy assessments.

Refined nanoscale platforms have enabled high-resolution structural analyses of misfolded proteins and ultrasensitive detection of early aggregates implicated in neurodegenerative pathology (Ansciaux et al., 2015; Guerrini et al., 2015; Pradhan et al., 2015; Rodriguez et al., 2015; Ruggeri et al., 2015; Zhou et al., 2015). Micro-electron diffraction at 1.4 Å resolution revealed a stacked β-sheet protofibrillar architecture within the NACore segment of α-synuclein (Rodriguez et al., 2015). Aggregation-induced colorimetric shifts in gold NP aggregation enabled quantification of Aβ(1–40) at sub-nanomolar levels (Zhou et al., 2015), while a fluorescent probed displayed intense emission upon fibril binding, providing high-contrast visualization (Pradhan et al., 2015; Zhu et al., 2018). Surface-enhanced Raman spectroscopy (SERS) using an Al(III)-coordinated chemoreceptor captured phenyl ring deformations indicative of oligomeric species (Guerrini et al., 2015). Nanosphere lithography yielded multiplexed gold-indium tin oxide substrates that integrated electrochemical readouts with localized surface plasmon resonance to monitor fibrillogenesis in real time (Cheng et al., 2015b). Peptide-functionalized ultrasmall SPIO NPs have also enabled noninvasive magnetic resonance imaging of Aβ deposits with high spatial precision (Ansciaux et al., 2015; Cheng et al., 2015a). Despite challenges such as nonspecific interactions in biological fluids, the convergence of spectroscopic, electrochemical, and plasmonic methodologies holds considerable potential for detecting oligomeric intermediates at ultra-low concentrations while elucidating structural determinants of misfolding.

Collectively, these convergent advances underpin an emerging theranostic paradigm that unites high-resolution diagnostics with precision-targeted nanotherapeutics for neurodegenerative disease intervention. Lipid-based carriers, including exosomes, cubosomes, and liposomes, deliver protective agents directly to the brain, while polymeric, dendrimeric, and albumin-based complexes offer tunable architectures for molecular cargo encapsulation, enhanced proteolytic stability, and simultaneous imaging (Chen et al., 2014). Metallic and carbon-based nanoplatforms, such as selenium, gold, and graphene, can disrupt aggregates and stimulate clearance pathways. Concurrently, advanced nanoscale platforms detect incipient oligomers and elucidate fibril architectures that guide inhibitor design. By merging precise diagnostic tools with targeted and multifunctional nanocarriers, these approaches offer significant promise for revolutionizing the treatment of AD, PD, and related neurodegenerative disorders (Srivastava et al., 2021). Continued interdisciplinary efforts are warranted to optimize *in vivo* validation and accelerate clinical translation.

Dynamic monitoring–therapy closed-loop system

Effective management of protein misfolding disorders such as AD increasingly depends on dynamic closed-loop systems that couple real-time monitoring with therapeutic feedback. Central to this strategy is the development of nanomaterials capable of penetrating the BBB and localizing to sites of pathology with high fidelity. As observed in previous studies, neutrophil membrane-coated, cerium-doped Prussian blue NPs (NM@PB-Ce, ~142 nm) with intrinsic catalase-, SOD-, and peroxidase-like activities reduced phosphorylated tau and inflammatory cytokines (IL-1β, IL-18) via inhibition of pyroptosis in an AD mouse model, following daily intraperitoneal injection of 320 μg/mL over 14 days (Ma et al., 2025b). Treated animals exhibited enhanced cognitive performance across Morris water maze, Y-maze, and open field tests, accompanied by lower NLRP3 levels and higher dendritic spine density. In another approach, MnO_2-based NPs functionalized with Aβ-targeting antibodies lowered amyloid plaque burden and improved cerebral glucose metabolism in TgCRND8 mice, as detected by [^{18}F]FDG-positron emission tomography (PET) (Park et al., 2025). Red blood cell (RBC) membrane-coated polycaprolactone nanocarriers encapsulating curcumin enhanced BBB transport eightfold in co-culture assays and mitigated $A\beta_{(25–35)}$-induced

cognitive deficits *in vivo* (Gu et al., 2024). Similarly, erythrocyte membrane-coated PLGA NPs functionalized with TGN peptide exhibited eightfold higher accumulation in excised brains and significantly improved recognition indices in behavioral paradigms (Gao et al., 2020b; Gregoretti et al., 2004; Yan et al., 2024). In parallel, cerium- and manganese-based nanosystems reduced ROS by approximately 80%, suppressing Aβ aggregation and oxidative damage (Hu et al., 2023). Collectively, these integrated platforms demonstrate the feasibility of BBB-penetrating nanotherapeutics that deliver concurrent molecular intervention, real-time imaging, and feedback-driven adjustment suitable for adaptive treatment paradigms.

Despite promising outcomes, translational challenges remain. Variability in BBB transcytosis efficiency across distinct AD models—many of which rely on artificially disrupted barriers or genetically modified strains—limits extrapolation to human neurovascular physiology and complicates standardization of quantitative metrics (e.g., accumulation fraction, reduced plaque burden). Experimental inconsistencies in animal background, dosing regimens, and imaging protocols further impede direct comparisons across studies. These limitations emphasize the need for *in situ* quantification frameworks capable of capturing nanomaterial transport under clinically relevant conditions rather than relying on surrogate markers. Nonetheless, advances in surface ligand engineering and physicochemical optimization suggest that robust targeting can be achieved, enabling real-time monitoring and synergistic treatment of protein aggregates and neuroinflammation.

Early-stage identification of protein aggregates and their associated biomarkers is essential for implementing responsive monitoring-therapy loops. A digital SERS platform with multiplexing capability enabled simultaneous tracking of $A\beta_{42}$ and $A\beta_{40}$ at single-NP resolution, achieving detection thresholds of 8.7×10^{-17} g/mL and 1.0×10^{-15} g/mL, respectively, using bumpy core-shell gold nanostructures that expanded the linear dynamic range by five orders of magnitude (Shim et al., 2025). These findings underscore the clinical importance of $A\beta_{42}/A\beta_{40}$ ratios in AD staging and demonstrate the potential of advanced Raman reporters for rapid and ultrasensitive multi-analyte detection. Complementary sensing modalities, such as ultra-sensitive photoelectrochemical biosensors based on g-C_3N_4, Au NPs, and TiO_2, exhibited a linear range of 10^{-15}–10^{-11} g/mL and a limit of detection of 0.33 fg/mL for $A\beta_{40}$ (Li et al., 2024e). Artificial intelligence-assisted SERS approaches demonstrated over 99% accuracy in differentiating AD patients from healthy controls based on metabolomic profiles (Kim et al., 2024). Electrochemical aptasensors incorporating polypyrrole, reduced GO, and Fe_2O_3 NPs achieved a detection limit of 40 fmol/L for $A\beta_{1–40}$ oligomers and demonstrated high selectivity in artificial serum (Fan et al., 2025). In comparison, unlabeled colorimetric aptasensors provide operational simplicity but typically exhibit higher detection thresholds in the nanomolar range, which limits sensitivity and makes them susceptible to interference from blood-derived components (Tu et al., 2023). Although the exceptional sensitivity achieved *in vitro* can be difficult to replicate clinically, biosensing technologies are rapidly advancing toward minimally invasive, high-throughput formats compatible with complex biological matrices. The incorporation of polyA or polyT linkers mitigates nonspecific adsorption, improving reliability. These innovations support real-time biomarker tracking and facilitate dynamic adjustments to NP dosing or formulations, enabling responsive and personalized therapeutic intervention.

In parallel with diagnostics, therapies targeting protein misfolding and neuroinflammation are essential for controlling AD progression. For instance, PLGA NPs reduced temperature-dependent tau aggregation by up to 90% *in vitro* and partially dismantled existing fibrils under disease-relevant heat stress (40°C) (Paul et al., 2025), as confirmed by Thioflavin T assays, transmission electron microscopy, and filter-trap analysis, implicating interference with tau hexapeptide motifs. Further analysis revealed that as temperatures increased from 27°C to 40°C, fibril formation accelerated and lag phases shortened, indicating heightened misfolding propensity; however, PLGA reduced aggregation rates by over 50% even under these conditions and partially reversed established fibrils (Paul et al., 2025). Although *in vitro* findings do not fully replicate *in vivo* complexities or tau isoform diversity, they demonstrate the potential for polymeric carriers to stabilize nontoxic intermediates. Other nanocarriers delivered gene components that down-regulated β-secretase 1 and curbed microglial hyperactivation in mouse models, ultimately improving cognition (Chen et al., 2025). Tetrahedral framework nucleic acids mitigated ferroptosis by lowering Fe^{2+} levels and enhancing GSH, reversing deficits in APP/PS1 mice (Tan et al., 2024). Additional strategies employed hierarchical antioxidant scaffolds, often doped with cerium or manganese, to quench ROS and disrupt Aβ assembly (Wang et al., 2024c; Zhang et al., 2024b), while promoting neuroprotective microglial phenotypes that reduced TNF-α, IL-1β, and IL-6 (Huang et al., 2023; Memo et al., 2024). These approaches may be particularly effective when integrated into a closed-loop system that continuously monitors biomarker fluctuations and adjusts NP composition or dosing in real time.

Physiologically relevant models have further clarified how nanoformulations traverse the BBB and modulate inflammatory pathways. A BBB-on-a-chip platform integrating human astrocytes, pericytes, and endothelial cells was established to replicate tight junction architecture and enable real-time transendothelial electrical resistance (TEER) measurements. Within this microfluidic system, GNR-PEG-Ang2/D1 constructs induced a transient TEER decrease, indicating successful barrier crossing, while GNR-PEG alone exhibited limited transmigration (Palma-Florez et al., 2023). Complementary approaches in optically transparent zebrafish with lipopolysaccharide (LPS)-driven neuroinflammation demonstrated that ferritin-loaded curcumin suppressed nitric oxide release and microglial infiltration (Chen et al., 2025). *Ex vivo* organotypic brain slices revealed that inflammatory signaling propagated through glia-derived extracellular vesicles (Memo et al., 2024) and that GO prevented astrocytic calcium dysregulation under cytokine exposure (Di Mauro et al., 2023). Although these models better recapitulate fluidic forces and multicellular crosstalk than single-cell assays, they remain constrained by cost, throughput, and incomplete representation of aging neural microenvironments. Nevertheless, convergent evidence supports continued progress toward dynamic monitoring-therapy closed-loop systems that address misfolded protein accumulation and neuroinflammation in AD. Biomimetic cerium-doped enzymes, polymeric carriers, nucleic acid frameworks, and gold-based constructs have demonstrated BBB penetration and disruption of Aβ or tau pathogenic pathways, while newly developed

biosensors—ranging from multiplexed SERS platforms to user-friendly aptasensors—have enabled earlier and more precise disease detection (Ouyang et al., 2022b). Integration of three-dimensional (3D) co-cultures, microfluidic BBB chips, and live-animal imaging further expand the toolkit for real-time feedback on misfolding and inflammation, bridging bench-scale discoveries and robust therapeutic outcomes. Although animal models and administration regimens vary across laboratories, the overarching trend features synergy between ultrasensitive biomarker detection and therapies that target both protein aggregation and excessive immune responses. This paradigm promises to optimize personalized AD interventions by calibrating nanocarrier design, dosing, or surface modifications in response to continuous biomarker readouts, ultimately providing a template for other complex neurodegenerative conditions.

Personalized intervention roadmap

Customized nanocarrier formulations enable more precise interventions in neurodegenerative diseases by aligning therapeutic strategies with individual pathological signatures, genetic predispositions, and biomarker profiles. Patients with AD or related neurodegenerative disorders exhibit divergent disease trajectories, heterogeneous BBB integrity, and distinct molecular indicators (Furtado et al., 2018; Huang & Mucke, 2012). Tailoring nanocarriers to specific pathophysiological mechanisms improves drug localization, enhances therapeutic efficacy, and minimizes off-target effects. Multimodal functionalization further permits targeted engagement of aberrant substrates, such as misfolded proteins and proinflammatory markers. For example, liposomes coated with CCR2-overexpressing cell membranes have directed therapeutic payloads to inflamed neural regions by exploiting elevated chemokine gradients. In individuals with high chemokine expression, conjugation to CCR2-binding ligands enhances local drug accumulation, while alternative nanocarrier designs can be adapted to other inflammatory cues. This precision-guided approach also supports rational design of co-encapsulation strategies, addressing multifactorial disease drivers such as protein aggregation and microglial activation through concurrent delivery of autophagy inducers and anti-inflammatory agents. By matching ligands and cargo to each patient's molecular profile, this paradigm achieves greater specificity and therapeutic control than uniform treatment schemes.

Beyond inflammation, nanocarrier properties, including size, surface charge, and release kinetics, can be adjusted to accommodate patient-specific BBB characteristics that vary with disease severity, genetic background, or comorbidities. In early disease with preserved barrier integrity, functionalization with transferrin or lactoferrin promotes receptor-mediated transcytosis. In contrast, later stages marked by barrier disruption may require delayed-release constructs to prevent nonspecific drug accumulation in peripheral organs (Chen et al., 2010). Genetic risk factors such as APOE4 in AD further accelerate Aβ plaque pathology and synaptic dysfunction (Gaiteri et al., 2016; Levi et al., 2007; Tolar et al., 1999), necessitating carriers engineered for accelerated delivery or enhanced brain retention. Similarly, individuals with elevated oxidative stress may benefit from formulations that incorporate antioxidants alongside anti-Aβ or anti-inflammatory agents, thereby addressing intersecting pathological axes. Although each adjustment may appear minor, they can substantially enhance therapeutic indices, stabilize cognitive trajectories, and reduce adverse side effects by harmonizing treatments with patient-specific molecular disruptions.

In parallel, advanced carrier platforms featuring modular compartments and stimulus-sensitive elements permit dynamic control over exposure and drug release, guided by longitudinal biomarker profiles or imaging feedback. These systems respond to local environmental changes—such as altered pH, elevated ROS, or enzyme activity within lesion sites—by modulating their release rates. Higher drug loads are released in regions of pronounced inflammation, while minimal delivery occurs in areas with limited pathology. This spatiotemporal responsiveness aligns therapy with evolving pathological states, particularly in neurodegenerative conditions where Aβ loads, tau pathology, and inflammatory signals fluctuate over time. Early-stage trials have indicated that patient-tailored formulations reduce off-target toxicity and adverse events by concentrating active agents at diseased sites, thereby lowering the required systemic dose. Emphasizing inter-individual heterogeneity over one-size-fits-all interventions has the potential to improve adherence, minimize systemic burden, and decelerate disease progression. Ultimately, individualized nanomedicine leverages genotypic and biomarker data, in combination with adaptive carrier designs, to optimize therapeutic impact at each disease stage.

Despite these advances, efficient drug delivery across the BBB remains a fundamental challenge in treating neurodegenerative disease (Reimold et al., 2008; Zhou et al., 2018). Numerous studies report strategies to improve CNS transport, such as calcium phosphate lipid NPs encapsulating antisense oligonucleotides to silence SOD1 in ALS (Ediriweera et al., 2025). In G93A-SOD1 transgenic mice, co-administration with focused ultrasound and microbubbles improved regional antisense oligonucleotide delivery, reduced SOD1 expression, and preserved motor neuron counts. MRI confirmed that BBB disruption was transient and non-destructive, supporting the feasibility of such approaches. Similarly, transferrin-functionalized mesoporous selenium nanocarrier delivering metformin improved cortical Aβ clearance and cognitive function in AD mice (Guo et al., 2025). Comparable strategies have been proposed for Huntington's disease, where high molecular weight lipid nanocarriers carrying engeletin traversed the BBB by mimicking endogenous lipid structures (Smriti et al., 2023). Although many findings stem from *in vitro* or rodent models, emerging data confirm that structurally optimized nanocarriers can achieve targeted delivery of small molecules and macromolecular payloads to the brain with improved specificity.

Beyond BBB transit, multiple studies have emphasized the importance of enhancing autophagy and lysosomal clearance to counter protein aggregation in diseases such as ALS and PD. For instance, in $SOD1^{G93A}$ ALS mice, a self-assembling lipidic formulation of PI(3, 5)P_2 (F1) extended survival by approximately 10 days by stabilizing the open state of TRPML1, thereby improving autophagy and reducing gliosis (Tedeschi et al., 2024). In Parkinsonian models, acidic NPs re-acidified lysosomes, limited protein accumulation, and restored dopaminergic neuron viability (Arotcarena et al., 2022). CeO_2 NPs slowed aggregation processes by exploiting redox activity to restore lysosomal function and stimulate autophagy (Pérez Gutiérrez et al., 2024). Metal-based and

hybrid NPs also directly neutralize misfolded proteins, a primary trigger for microglial activation. For example, bimetallic Au/Ag-NPs inhibited Aβ aggregation more effectively than single-metal counterparts (Gülseren et al., 2024); silver NPs suppressed α-lactalbumin fibril assembly in a dose-dependent manner (Dehvari & Ghahghaei, 2018); and gold-based hybrid photosensitizers increased singlet oxygen generation to hamper tau aggregation (Liao et al., 2012; Palmal et al., 2014; Wei et al., 2024). Concerns regarding toxicity are being addressed through greener synthesis and biocompatible surface coatings, such as polyglycerol or amino acid-based shells (Rauf et al., 2022). Immune modulation further complements these strategies by targeting microglial dysfunction. For example, ferulic acid and tannic acid NPs reduced intracellular ROS and cytokine release in microglia challenged with α-synuclein, while nanoscale α-mangostin rejuvenated microglial clearance in AD and PD models (Wang et al., 2023c; Zhao et al., 2020). Advanced characterization methods, including tip-enhanced Raman spectroscopy (TERS), enable real-time detection of the most toxic protein assemblies, guiding more precise NP design (Lipiec et al., 2018; Mandal et al., 2023; Sreeprasad & Narayan, 2019). Collectively, these strategies converge on multifunctional nanocarriers that integrate targeted transport, anti-aggregate potency, and immune modulation to address neurodegeneration from multiple mechanistic angles. Continued progress in carrier design, mechanistic insight, and preclinical validation remains essential for translating these multidimensional nanotherapies into effective clinical therapies.

CURRENT CHALLENGES AND FUTURE DIRECTIONS

Nanomaterial-based therapies hold significant potential for addressing protein misfolding and neuroinflammation in neurodegenerative diseases. However, clinical translation remains constrained by several persistent challenges. A key barrier is the difficulty in scaling nanocarrier production from controlled laboratory conditions to industrial manufacturing, where variations in synthesis parameters frequently lead to inconsistent particle size, surface charge, and drug-loading efficiency. These physicochemical inconsistencies can significantly alter pharmacokinetics, therapeutic efficacy, biodistribution, and safety, thereby complicating efforts to standardize treatment regimens and predict clinical outcomes. Consequently, the progression of nanotherapeutics from preclinical models to clinical application is critically dependent on a comprehensive understanding and validation of their safety and performance profiles. While the functional versatility of nanomaterials supports novel therapeutic strategies, their unique surface chemistry, high reactivity, and nanoscale dimensions also raise substantial concerns regarding their toxicology. Ensuring both efficacy and safety requires comprehensive assessment of biocompatibility, biodistribution, and long-term biological impact to navigate regulatory requirements and support clinical deployment.

Among the most critical concerns surrounding the use of nanomaterials in biological systems is potential nanotoxicity, arising from their intrinsic physicochemical properties. Metallic and inorganic NPs, in particular, are associated with excessive ROS production, which can trigger oxidative stress, disrupt cellular components, impair lysosomal function, and induce DNA and protein damage. These effects not only compromise cellular homeostasis but may also exacerbate neuroinflammatory responses—the very pathologies these therapies aim to suppress. Experimental evidence indicates that NP exposure can lead to heightened cytokine release, autophagic dysregulation, and membrane destabilization, often culminating in necrotic cell death. Such adverse outcomes are frequently driven by high surface-to-volume ratios and surface reactivity, which can catalyze deleterious biochemical reactions.

The toxic potential of NPs is governed by the combined influence of their physical and chemical attributes. Key determinants include particle size, composition, surface charge, and surface chemistry. Smaller particles, such as silver NPs with diameters around 15 nm, exhibit greater toxicity and hemolytic activity than larger formulations (Chenthamara et al., 2019; Lahiani et al., 2017; Morales-Avila et al., 2017). Surface charge also influences toxicity, with cationic particles generally exhibiting stronger cytotoxicity than neutral or anionic variants due to their non-specific electrostatic interactions with negatively charged cell membranes (Chenthamara et al., 2019; Miao et al., 2024; Waris et al., 2022). Material composition further shapes toxicity profiles, as polymer-based systems such as PLGA are widely considered biocompatible and biodegradable, whereas certain metal- or metal oxide-based NPs may pose greater toxicological risks. These risks can be mitigated by rational surface engineering, as illustrated by poly(acrylic acid)-coated AuNPs, which demonstrate protective properties in cellular environments.

Beyond immediate cytotoxic responses, long-term biocompatibility and biodistribution of nanomaterials are essential for their safe application in chronic conditions like neurodegenerative diseases. A comprehensive understanding of post-administration dynamics—including cerebral clearance and unintended deposition in peripheral organs such as the liver, spleen, and kidneys—is necessary to anticipate and prevent long-term adverse effects. Persistent accumulation of non-biodegradable NPs may provoke chronic inflammation, disrupt tissue homeostasis, or initiate pathological remodeling. Consequently, the design of nanomaterials from biodegradable components, such as PLGA, offers a strategic foundation for reducing persistence-related risks. However, careful investigation of the degradation process and the potential toxicity of any byproducts is a mandatory step in preclinical safety assessment.

Ultimately, successful clinical translation depends on navigating stringent regulatory frameworks. The distinct properties of nanomedicines require specialized preclinical evaluation beyond traditional toxicology assays, including comprehensive characterization of cytotoxicity, immunogenicity, and hemocompatibility, as well as detailed pharmacokinetic and pharmacodynamic profiles related to absorption, distribution, metabolism, and excretion. Future research should prioritize the development of inherently safe and biocompatible NPs with predictable degradation profiles and minimal off-target effects. A safety-by-design approach is essential for bridging the gap between laboratory success and clinical application in neurodegenerative disease therapeutics.

Chronic neuroinflammation is a hallmark of neurodegenerative disease progression, maintained through a dynamic interplay between CNS pathology and peripheral immune dysregulation (Moghaddam et al., 2021; Obrador et al., 2020; Solleiro-Villavicencio et al., 2018). Accordingly, emerging therapeutic strategies increasingly extend beyond

direct neuronal intervention to include modulation of the immune environment. Nanomaterials represent a sophisticated and versatile platform for such strategies, offering the capacity to regulate immune responses and thereby exert secondary neuroprotective effects. This immunomodulatory potential can be directed toward suppressing maladaptive inflammatory cascades or dismantling upstream triggers of inflammation. One major approach involves the use of NPs with intrinsic anti-inflammatory properties or those engineered for targeted delivery of immunomodulatory compounds. For instance, silver-based NPs have been shown to reduce systemic levels of proinflammatory cytokines like TNF-α and interferon-γ, both of which exacerbate neuroinflammation. Similarly, curcumin-loaded NPs have shown enhanced efficacy in neutralizing Aβ-induced cytotoxicity by modulating inflammatory pathways. In addition to active suppression, nanomaterials can indirectly modulate the immune system by dismantling pathogenic protein aggregates. Misfolded protein deposits, such as Aβ plaques, act as chronic stimuli for microglia and astrocytes. Agents such as gold-based NPs capable of amyloid fibril disaggregation, or coenzyme Q10-loaded formulations that diminish senile plaque burden, disrupt the self-amplifying cycles of neuroinflammation by eliminating the initiating insult.

Despite these advantages, the immunomodulatory effects of NPs are highly dependent on their physicochemical attributes and can provoke unintended immune activation. Parameters such as size, surface charge, composition, and coating dictate interactions with innate and adaptive immune components. Without appropriate design for biocompatibility, nanomaterials may be identified as immunogenic, eliciting acute inflammatory responses that undermine therapeutic efficacy and exacerbate systemic or central pathology (Jia et al., 2009; Kermanizadeh et al., 2013; Kus-Liśkiewicz et al., 2021). Effective mitigation requires precise control over surface functionalization and rigorous manufacturing consistency. While surface modifications can prolong particle circulation and enhance targeting, they may also introduce epitopes or contaminants capable of triggering immune recognition (Jokerst et al., 2011; Xia et al., 2019; Zamora-Justo et al., 2019). The development of immunologically inert or “stealth” formulations—through hydrophilic coatings, zwitterionic surfaces, or selective ligand shielding—has become a critical design priority. Such modifications are essential for ensuring therapeutic delivery to the CNS without inciting immune clearance or collateral inflammation (Jia et al., 2013; Martín-Rapun et al., 2017; Oh et al., 2018).

In parallel with managing immunogenicity, efficient transport across the BBB remains a significant hurdle. Although receptor-, adsorptive-, and ligand-mediated transcytosis strategies can improve NP delivery to the brain, their success is often constrained by dynamic alterations in BBB integrity during disease progression (Popov et al., 2013). In early-stage AD, for instance, the BBB generally retains its restrictive properties, impeding the passage of large carriers. In contrast, advanced stages may present with a more permeable barrier, increasing CNS exposure to circulating inflammatory mediators (Nation et al., 2019; Stanić et al., 2017). Accordingly, preclinical and early clinical trials must rigorously verify that targeted nanoplatforms reach pathologically relevant regions without compromising healthy tissue or triggering adverse immune reactions that outweigh therapeutic benefits.

As targeted transcytosis methodologies evolve, preclinical assessments in rodent and large-animal models remain essential to validate therapeutic outcomes and off-target profiles. Longitudinal assessments of survival, histopathology, cognitive performance, and immune activation are critical to determine whether nanotherapeutics exert genuine neuroprotective effects or merely modulate biomarkers without altering disease trajectory. Current research increasingly emphasizes multifunctional nanoplatforms engineered to address convergent pathological mechanisms. These next-generation scaffolds may incorporate anti-aggregative peptides, nucleic acid therapeutics, and anti-inflammatory agents within modular scaffolds, often coupled with imaging tracers or fluorescent tags for real-time biodistribution and efficacy monitoring. However, despite promising outcomes in preclinical settings, most of these complex, multifunctional constructs remain confined at the *in vitro* or proof-of-concept stage. The integration of biomarker-driven strategies could further personalize approaches by matching specific nanoformulations to disease stage or molecular signatures, providing feedback via quantitative tracking of misfolded proteins or inflammatory markers to optimize therapeutic delivery and dosing.

In AD and related neurodegenerative disorders, the failure of conventional therapeutics is often attributable to the multifactorial nature of disease and the limited penetrance of therapeutic agents across the BBB (Huang & Mucke, 2012; Nation et al., 2019; Saraiva et al., 2016). While barrier disruption may occur during disease progression, this does not reliably translate into enhanced drug access to target regions. In response, numerous nanoparticle-based systems are under investigation for their structural stability, surface versatility, and capacity to co-deliver synergistic agents (Rodriguez-Otormin et al., 2019; Ulanova et al., 2020).

Combinatorial approaches that simultaneously target Aβ deposition, tau aggregation, and neuroinflammatory processes offer the potential for more comprehensive disease modification. Translating these platforms into clinical use will require rigorous particle characterization, precise biomarker integration, and adherence to GMP standards to ensure safety, reproducibility, and therapeutic efficacy across heterogeneous patient populations affected by AD, ALS, PD, and other neurodegenerative conditions.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS’ CONTRIBUTIONS

X.L.Q. provided ideas and outlines. Y.H.W. and X.L.L. collected references and prepared the original manuscript and figures. X.L.Q. supervised and Y.H.W. and X.L.L. revised the manuscript and figures. All authors read and approved the final version of the manuscript.

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