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REVIEW

Nanotechnology for Neurodegenerative Diseases: Recent Progress in Brain-Targeted Delivery, Stimuli-Responsive Platforms, and Organelle-Specific Therapeutics

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Abstract: Neurodegenerative diseases—including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis—are characterized by progressive neuronal loss and complex pathological mechanisms such as protein aggregation, mitochondrial dysfunction, and neuroinflammation. Conventional therapies offer limited efficacy due to the blood–brain barrier (BBB) and lack of targeted delivery. Nanotechnology has emerged as a transformative strategy for precise brain-targeted treatment. This review summarizes recent advances in nanoparticle-based drug delivery systems, including polymeric nanoparticles, liposomes, inorganic nanomaterials, and biomimetic carriers, highlighting their design features, BBB-penetration mechanisms, and disease-specific applications. Emphasis is placed on stimuli-responsive nanocarriers that react to pH, reactive oxygen species, or enzyme activity, enabling site-specific drug release. Additionally, organelle-targeting strategies—particularly those directed at mitochondria and lysosomes—are explored for their role in subcellular precision therapy. The integration of diagnostic and therapeutic modalities in theranostic nanoplatforms is also discussed. By consolidating preclinical progress and emerging technologies, this review offers insights into the future of nanomedicine in treating neurodegenerative diseases and lays the groundwork for clinical translation.

Keywords: blood–brain barrier penetration, stimuli-responsive nanocarriers, gene therapy, theranostic nanoplatforms

Introduction

Neurodegenerative diseases (NDs) are a group of chronic, progressive disorders characterized by the sustained degeneration and loss of neurons within the central nervous system (CNS). Representative conditions include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). These disorders are typically marked by region-specific neuronal loss, accompanied by complex pathological processes such as abnormal protein aggregation, synaptic dysfunction, mitochondrial impairment, and chronic neuroinflammation.[1,2] With the rapid aging of the global population, the incidence of NDs is steadily rising, making them a major contributor to disability and mortality among the elderly.[3]

Although the precise pathogenesis of NDs remains elusive, they share common features of insidious onset, prolonged disease course, and multifactorial etiology. Current therapeutic strategies are largely symptomatic, with drugs such as donepezil, levodopa, and riluzole providing only limited symptom relief without halting or reversing disease progression.[4–8] Moreover, the presence of the highly selective blood–brain barrier (BBB) in the CNS significantly impedes drug penetration, resulting in subtherapeutic concentrations within brain tissues and limiting treatment efficacy.[9–11]

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In recent years, the advent of nanotechnology has opened new avenues for the precision treatment of neurodegenerative diseases. Nanoparticle-based drug delivery systems (NDDSs), characterized by their nanoscale architecture, are capable of efficiently encapsulating, transporting, and releasing therapeutic agents in a controlled manner. These platforms provide excellent biocompatibility, tunable engineering properties, and multifunctional surface modification capabilities.[12,13] Compared to conventional formulations, nanocarriers can cross the BBB via various mechanisms such as adsorptive-mediated transcytosis (AMT) and receptor-mediated transcytosis (RMT), enabling passive or active targeting to diseased regions and enhancing local drug concentrations.[14] Furthermore, NDDSs can be designed with pH-, reactive oxygen species (ROS)-, or enzyme-sensitive mechanisms to achieve environment-responsive controlled release, thereby minimizing systemic toxicity and adverse effects.[15] Some advanced platforms also integrate theranostic functionalities, combining therapeutic delivery with imaging modules—such as MRI, PET, or fluorescent probes—for real-time disease monitoring and therapeutic evaluation.[16,17]

Despite encouraging results from preclinical studies, the clinical translation of NDDSs continues to face significant challenges, including inconsistent delivery efficiency, insufficient biosafety assessments, complex manufacturing processes, and difficulties in large-scale production.[13,18] This review aims to provide a comprehensive overview of the major types of nanoplatforms currently employed in the treatment of NDs, highlighting their structural features, BBB penetration capabilities, targeting mechanisms, delivery strategies, and therapeutic outcomes across representative diseases such as AD, PD, HD, and ALS. Additionally, we will discuss emerging trends in stimuli-responsive systems (eg, pH-, ROS-, and enzyme-sensitive designs) and organelle-targeted platforms (eg, mitochondria, lysosomes), while evaluating the design principles and translational prospects of theranostic systems. This review seeks to provide a theoretical foundation and practical framework to support the precision intervention and clinical application of nanotechnology in neurodegenerative diseases.

Nanocarrier Systems and Strategies for Blood–Brain Barrier Penetration

Neurodegenerative diseases are characterized by complex etiologies, prolonged progression, and multifactorial pathogenesis, which not only complicate therapeutic interventions but also limit drug penetration into the brain due to the formidable BBB. In recent years, advances in nanotechnology have opened new opportunities for enabling BBB crossing and targeted drug delivery to the central nervous system. The selection of an appropriate nanocarrier and the full exploitation of its structural and functional advantages are prerequisites for achieving efficient delivery and precise therapeutic effects. Therefore, before discussing disease-specific diagnostic and therapeutic strategies, it is essential to provide a systematic overview of the various types of nanocarriers, their physicochemical properties, and BBB penetration strategies, which lays the foundation for subsequent application and mechanistic analyses.

Nanocarrier Types and Characteristics

Nanocarrier systems form the cornerstone of precise drug delivery to the central nervous system, playing a pivotal role in enhancing brain-targeting efficacy. In the treatment of neurodegenerative diseases, nanoparticle-based drug delivery platforms are generally categorized into four major types based on their material composition and functional properties: polymeric nanoparticles, liposomes, inorganic nanoparticles, and biomimetic nanoparticles. Each class provides distinct advantages in terms of structural design, drug-loading capacity, biocompatibility, and ability to traverse the blood–brain barrier, making them suitable for diverse therapeutic strategies.

Polymeric nanoparticles are among the most extensively employed delivery systems, owing to their excellent biodegradability, drug-loading stability, and capacity for controlled release. Commonly composed of biodegradable polymers such as PLGA, PEG, and chitosan, these carriers exhibit outstanding biocompatibility and facilitate sustained drug release.[19,20] By fine-tuning particle size, surface charge, and functional moieties, they can be optimized for the efficient delivery of small molecules, proteins, peptides, and nucleic acids such as siRNA and ASOs.

For instance, Huang et al developed a PLGA-based nanocarrier system co-encapsulating a β-amyloid (Aβ) formation inhibitor and curcumin. Surface modification with the brain-targeting CRT peptide enhanced its permeability across the blood–brain barrier.[21] In Alzheimer's disease mouse models, this system significantly improved spatial learning and memory, reduced Aβ plaque burden and neuroinflammation, thereby demonstrating promising potential in multi-targeted therapeutic interventions. Similarly, Shin et al designed PLGA nanoparticles loaded with p16Ink4a-siRNA to specifically

target and reprogram senescent microglia. By downregulating p16Ink4a expression, the system restored microglial phagocytic function, markedly improved Aβ clearance, and ameliorated cognitive deficits in 5XFAD Alzheimer's mice.[22] This study provided the first evidence that functional remodeling of immune cells via nanocarrier-mediated delivery could effectively intervene in the core pathologies of Alzheimer's disease.

These findings underscore the capacity of polymeric nanocarriers in addition to ensuring stable drug delivery and BBB penetration, but also to enable intelligent design for multi-target therapy and immune modulation. Such systems provide novel strategies and translational prospects for the treatment of neurodegenerative diseases like Alzheimer's.

Liposomes, which mimic the architecture of biological membranes through their phospholipid bilayer structure, can simultaneously encapsulate both hydrophilic and hydrophobic drugs. With high biocompatibility and low immunogenicity, liposomes were among the first nanocarriers approved for clinical use. In neurodegenerative disease research, they are widely applied for delivering neuroprotective agents such as dopamine and curcumin, significantly enhancing drug stability and prolonging therapeutic retention within brain tissue.

In recent years, a growing body of experimental evidence has confirmed the remarkable advantages of liposomes in delivering therapeutics to the central nervous system. For example, Campisi et al developed curcumin-loaded solid lipid nanoparticles (CUR-SLNs) to mitigate stress and inflammatory responses in AD mouse models.[23] By modulating the expression of tissue transglutaminase (tTG) isoenzymes, this system significantly improved mitochondrial function and cognitive performance, suggesting that liposomes in addition to ensure superior drug stability but also exert neuroprotective effects through modulation of neuroinflammatory signaling pathways. Additionally, Zhang et al designed a drug-pure liposomal platform for intranasal delivery aimed at modulating microglial polarization in AD mice.[24] The system effectively promoted M2 phenotype polarization and suppressed pro-inflammatory cytokine expression, thereby reducing neuroinflammation and enhancing learning and memory, demonstrating the translational potential of liposomes in non-invasive brain-targeted therapies. In Parkinson's disease research, Sela et al developed a brain-targeted liposomal system carrying anti-α-synuclein monoclonal antibody SynO4, utilizing receptor-ligand modification to improve BBB permeability.[25] This system significantly reduced α-synuclein aggregation and improved motor performance, underscoring the effectiveness of liposomes in delivering macromolecules and modulating neurodegenerative pathways.

In summary, liposomal nanocarriers, with their biomimetic membrane structures, excellent biocompatibility, and versatile drug-loading capacities, have demonstrated outstanding drug delivery efficiency and neuroprotective effects in models of AD and Parkinson's disease, indicating broad application prospects for neurological disorders.

In comparison, inorganic nanoparticles such as gold nanoparticles, iron oxide nanoparticles, and mesoporous silica nanostructures have attracted increasing attention in recent years for their theranostic potential in neurodegenerative diseases. Their advantages include structural stability, large surface area, multifunctionality (magnetic, optical, or chemical), and high potential for engineered modification. Each type provides specific benefits for molecular imaging enhancement, targeted drug delivery, and intervention in pathological mechanisms.

For imaging diagnostics, superparamagnetic iron oxide nanoparticles (SPIONs) exhibit excellent MRI enhancement capabilities. Ulanova et al developed DMSA-coated Fe_3O_4 nanoparticles modified with anti-Aβ antibodies to enable targeted recognition of Aβ plaques in AD brains.[26] In 5×FAD mice, this system significantly enhanced T_2-weighted MRI signals, provided strong imaging contrast at lesion sites, and demonstrated high biocompatibility in multi-organ toxicity assessments, providing a novel tool for early and precise diagnosis of AD.

In another study, Fe_3O_4 nanoparticles were encapsulated with hyaluronic acid to form magnetically responsive nanogels (Fe_3O_4-HyA), combining imaging capability with therapeutic function.[27] The system retained magnetic responsiveness and leveraged hyaluronic acid's targeting ability to enhance brain tissue accumulation. In vitro studies demonstrated it could inhibit Aβ1-42 aggregation and induce partial fibril disassembly, establishing a foundation for integrated diagnostic and therapeutic applications.

Gold nanoparticles (AuNPs), known for their exceptional optical properties and functionalization flexibility, have also demonstrated efficacy in Aβ aggregation inhibition and brain drug delivery. The AuNPs@POM@PEG system designed by Perxés et al inhibited over 75% of Aβ1-42 aggregation in vitro and demonstrated excellent BBB permeability in both a microfluidic BBB-on-chip model and in vivo mouse studies.[28] The system significantly reduced cerebral Aβ burden and improved cognitive behavior, highlighting its integrated therapeutic and delivery potential.

Mesoporous silica nanoparticles (MSNs), with their tunable pore sizes and high drug-loading capacity, have also demonstrated promise for sustained treatment of AD. Ribeiro et al loaded curcumin into MSNs and encapsulated them within a thermosensitive hydrogel to form a slow-release system.[29] In AD model mice, a single implantation enabled sustained drug release for six weeks, significantly improved cognitive function, and reduced both Aβ deposition and oxidative stress, validating the system's potential for long-term disease management.

Collectively, current experimental evidence strongly supports the multifunctional capabilities of inorganic nanomaterials in enabling brain-targeted delivery, enhancing lesion imaging, and modulating disease pathology. In various AD animal models, these materials have demonstrated both therapeutic efficacy and high biocompatibility, providing a solid material foundation for constructing integrated platforms for diagnosis, treatment, and real-time visualization. Their broad potential in the personalized treatment of Alzheimer's disease is evident.

Biomimetic nanocarriers have recently emerged as a promising class of delivery systems. By coating conventional nanoparticles with natural cell membranes—such as those from neurons, red blood cells, or stem cells—these systems acquire "self-recognition" immune evasion, and brain-targeting capabilities. With favorable biodistribution and high brain-targeting efficiency, they are particularly suitable for delivering siRNAs, antibodies, or neurotrophic factors.

For instance, Wang et al developed a biomimetic vesicle platform derived from cell membranes that co-delivers BACE1-targeted siRNA and a plasmid encoding the Triggering Receptor Expressed on Myeloid cells 2 (TREM2).[30] This system modulated microglial polarization in AD mouse models, reduced Aβ plaque deposition, alleviated inflammation, and significantly improved cognitive performance, demonstrating synergistic advantages in multi-target genetic interventions. Tang et al further developed functionalized biomimetic nanoparticles (HM-DK@CM) capable of crossing the BBB and selectively accumulating in brain lesions.[31] In AD models, these particles simultaneously inhibited Aβ aggregation and tau phosphorylation, alleviated neuronal pathology, and enhanced spatial learning and memory, affirming their potent therapeutic efficacy.

In ALS research, Huang et al constructed a biomimetic nanoplatform (Protein-HA-PRTM-rHDL) combining high-density lipoprotein structure with extracellular matrix elements for the efficient brain delivery of therapeutic proteins.[32] This system crossed the BBB and accumulated in diseased regions, significantly delayed motor function decline, and prolonged survival in ALS model mice, providing a novel paradigm for protein-based therapies in neurodegeneration.

In conclusion, biomimetic nanoplatforms, owing to their membrane-derived architecture, demonstrate excellent brain-targeting capacity, immune evasion properties, and multifunctional drug-loading potential. They have achieved efficient brain delivery and pronounced neuroprotective effects in models of AD and ALS. Experimental evidence underscores their broad adaptability in gene therapy, anti-protein aggregation, and neurotrophic factor delivery, revealing their immense translational potential for precise and personalized treatment of neurological disorders.

Simultaneously, different nanocarrier types possess distinct advantages in structural configuration, biocompatibility, drug-loading capacity, and delivery characteristics. Given the multifaceted pathogenesis and therapeutic challenges of neurodegenerative diseases, the rational selection or synergistic integration of polymeric, liposomal, inorganic, and biomimetic systems—combined with targeting strategies, stimuli-responsive release, and multifunctional modifications—can maximize drug delivery efficiency and therapeutic precision. Moving forward, advancing these platforms toward high efficiency, safety, scalable production, and clinical translatability will be essential for bridging the gap between laboratory research and clinical application in nanomedicine for neurodegenerative diseases.

To facilitate a clearer comparison of the performance, structural attributes, and mechanisms of BBB penetration among different nanocarriers, Table 1 provides a systematic summary of the main features and permeability profiles of polymeric nanoparticles, liposomes, inorganic nanomaterials, and biomimetic systems, providing a theoretical reference for strategy selection and design optimization in drug delivery systems.[33–39]

Mechanisms of Blood–Brain Barrier Penetration and Nanostrategies

The blood–brain barrier is a highly selective interface located between the capillaries of the brain and spinal cord and the surrounding neural tissue. It is composed of non-fenestrated endothelial cells, tight junction proteins, a basal lamina, pericytes, astrocytes, and an exceptionally narrow extracellular space. This intricate structure plays a critical role in maintaining central nervous system homeostasis but simultaneously restricts the entry of over 98% of pharmacological agents into the brain, thereby presenting a formidable obstacle to the effective delivery of therapeutics for neurodegenerative diseases.[9,40]

Table 1 Comparative Overview of Structural Characteristics, Mechanisms of Blood–Brain Barrier Penetration, and Relative Permeability of Various Nanocarriers

Nanocarrier Type	Structural/Compositional Features	Main BBB Penetration Mechanisms	BBB Potential Ability (Relative)	References
Polymeric nanoparticles (eg, PLGA, PLGA-PEG)	Biodegradable polymers with tunable particle size, surface charge, and flexible functionalization	Receptor-mediated transcytosis (RMT, eg, TfR, LRP), cell-penetrating peptides (CPP, eg, TAT), adsorptive-mediated transcytosis (AMT)	★★★★	[21–25,36,37]
Liposomes	Spherical vesicles composed of one or more phospholipid bilayers, capable of encapsulating both hydrophilic and lipophilic drugs, biocompatible and low immunogenicity	Receptor-mediated transcytosis (RMT, eg, via transferrin or lactoferrin), membrane fusion, and intranasal nose-to-brain delivery	★★★★	[26–28,38–40]
Inorganic nanoparticles (eg, Fe_3O_4, AuNPs, MSNs)	High surface area with tunable physical properties; support multifunctional integration for imaging and therapeutic delivery; commonly functionalized with targeting ligands or polymers (eg, PEG, antibodies)	Receptor-mediated transcytosis (RMT), cell-penetrating peptides (CPP), microenvironment-responsive mechanisms (eg, pH-sensitive or redox-sensitive release)	★★★★	[29–32]
Biomimetic nanocarriers (eg, cell membrane-coated nanoparticles)	Nanoparticles camouflaged with natural cell membranes (eg, erythrocytes, stem cells), providing immune evasion, extended systemic circulation, and BBB-targeted delivery	Biomimetic recognition, receptor-mediated transcytosis (RMT), and exosome-like or membrane fusion-mediated transport	★★★★★	[33–35,41,42]

Notes: This table presents a comparative summary of four major types of nanocarrier systems commonly employed in the treatment of neurodegenerative diseases: polymeric nanoparticles, liposomes, inorganic nanomaterials, and biomimetic membrane-based nanoparticles. The comparison encompasses structural composition, principal mechanisms for crossing the blood–brain barrier, and relative permeability. Drawing on data from relevant literature, this compilation aims to provide a theoretical reference for the rational design and optimization of nanocarrier platforms tailored to specific therapeutic needs. Blood–brain barrier permeability is represented using a star-rating system (★–★★★★★), indicating the relative strength of each carrier's performance.

Additionally, the presence of diverse enzymatic systems within cerebral endothelial cells constitutes an "enzymatic barrier" further hindering drug permeation and representing another physiological blockade to brain-targeted therapy.

To overcome these barriers, a variety of strategies have been developed to enhance the BBB permeability of nanocarriers, primarily involving the following mechanisms:

(1) Adsorptive-mediated transcytosis: This mechanism relies on electrostatic interactions between positively charged nanocarriers and the negatively charged endothelial membrane, triggering nonspecific endocytosis. Cationic polymers such as chitosan are commonly employed to construct such carriers, enabling a certain degree of BBB penetration. However, this strategy suffers from low specificity and may result in off-target accumulation in peripheral organs, compromising targeting accuracy and biosafety.[41]

(2) Receptor-mediated transcytosis: Currently the most widely adopted and efficient brain-targeting mechanism, RMT utilizes the conjugation of specific ligands—such as transferrin, lactoferrin, insulin, ApoE, or Rabies Virus Glycoprotein (RVG) peptides—on the nanocarrier surface. These ligands bind to corresponding receptors on brain endothelial cells, initiating receptor-mediated intracellular transport. RMT provides excellent selectivity and targeting efficiency and has been extensively applied in various neurological disease models.[42–44]

(3) Carrier-mediated transport and cell-penetrating peptide strategies (CPPs): Some nanocarriers exploit transporters for endogenous substrates (eg, glucose, amino acids) or are conjugated with cell-penetrating peptides like TAT or Penetratin to induce nonspecific endocytosis, thus broadening the mechanisms and applicability of BBB penetration.[45–47]

(4) Surface modification and functional design: To further enhance brain specificity and nanocarrier stability, strategies incorporating peptide or glycan ligand modifications have been employed to improve selectivity. Concurrently,

environmental-responsive modules—such as pH-, oxidative stress-, or enzyme-sensitive components—are integrated to enable controlled, site-specific drug release. For instance, Guo et al designed a dual-functional peptide (TPL), comprising TGN and Tet1, to modify nanoparticles for efficient BBB penetration and neuron-specific targeting. In AD mouse models, this system exhibited notable brain accumulation and neuroprotection. Additionally, peptide-functionalized nanoparticles with pH-responsive elements have been developed to achieve lesion-specific drug release and enhanced therapeutic outcomes.[48] Another innovative strategy involves coating nanoparticles with exogenous cell membranes—such as those from red blood cells, stem cells, or neurons—to construct biomimetic systems. These enhance immune evasion, prolong circulation time, and improve BBB translocation efficiency.[49]

Together, these mechanisms constitute the foundational strategies by which nanomedicines traverse the BBB. Each pathway is associated with unique nanocarrier types, surface engineering techniques, and transport channels, providing distinct advantages and application scenarios. In practice, these approaches are often combined to synergistically boost delivery efficiency and targeting precision. Figure 1 provides a schematic overview of the primary BBB penetration mechanisms and representative nanocarrier systems, serving as an intuitive reference for the future design and optimization of drug delivery platforms.

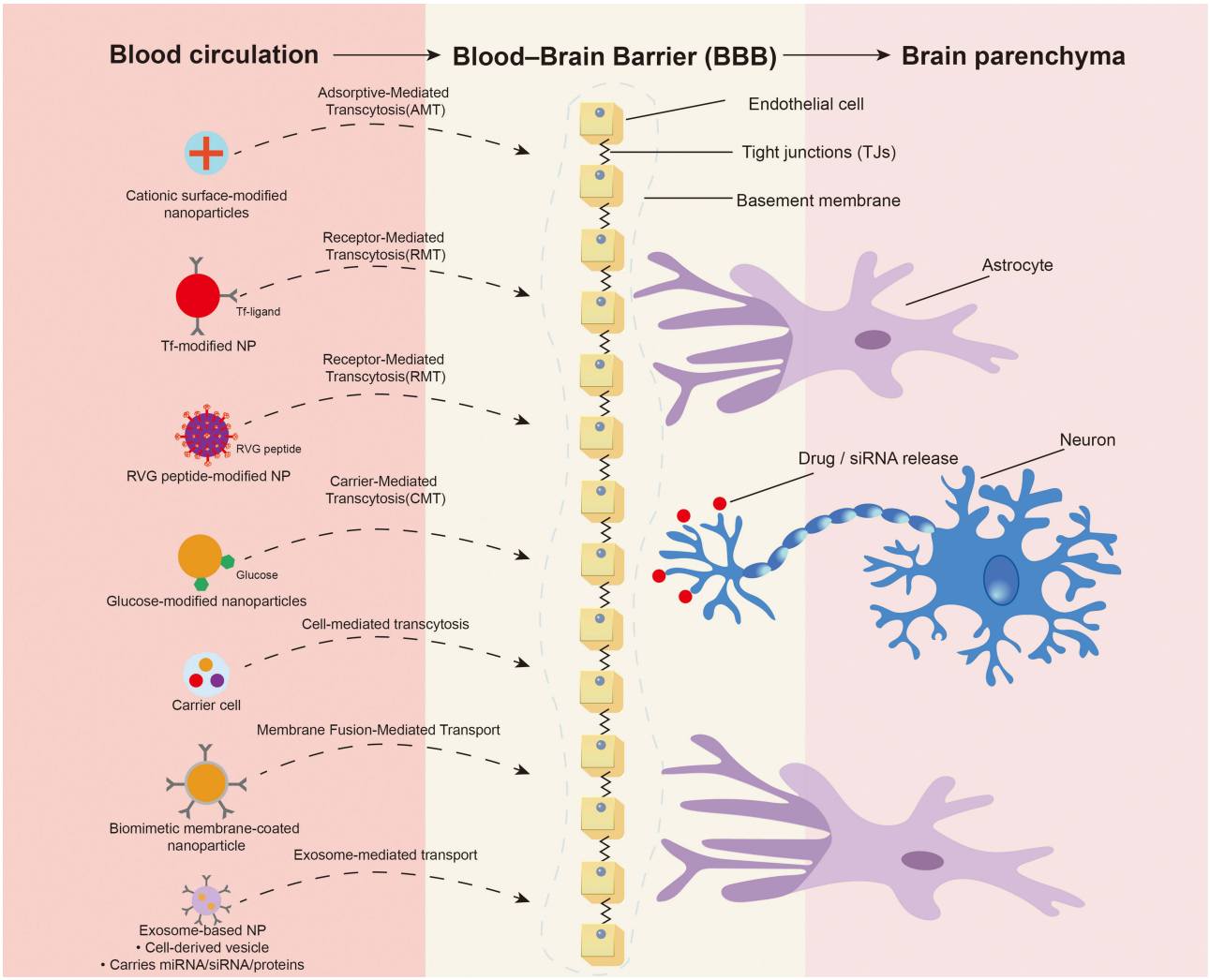

Figure 1 Principal Mechanisms and Representative Nanocarrier Strategies for Blood–Brain Barrier Penetration. Nanomedicines can cross the BBB via multiple mechanisms, including AMT, receptor-mediated transcytosis, carrier-mediated transport (CMT), cell-mediated transcytosis, membrane fusion, and exosome-mediated pathways. Each route corresponds to specific types of nanocarriers—for instance, those with cationic surface modifications, transferrin or RVG peptide conjugation, glycosylation, cell membrane coatings, or exosome-derived vesicles. Once traversing the BBB, these systems deliver therapeutic payloads (eg, small molecules or siRNAs) to neurons or glial cells, enabling effective treatment of neurological disorders.

In summary, research on nanocarrier-based BBB penetration has evolved from early passive diffusion strategies toward more active, tunable, and precisely engineered multi-mechanism approaches. Whether through receptor-ligand mediated transcytosis or microenvironment-responsive release triggered by stimuli such as pH shifts, oxidative stress, or enzymatic activity, the structural configuration and functional modification of nanocarriers remain central determinants of their capacity to cross the BBB and achieve precise therapeutic action in brain-targeted regions. Moving forward, a critical challenge will be to simultaneously enhance delivery efficiency while ensuring systemic stability, biocompatibility, and long-term safety. Addressing this challenge will be essential for advancing nanocarrier platforms from preclinical research to clinical translation in the treatment of neurodegenerative diseases.

Advances in Disease-Specific Applications of Targeted Nanocarrier Systems

With the continuous evolution of nanomedicine in the treatment of neurodegenerative diseases, nanocarrier-based drug delivery systems have emerged as a promising solution to address long-standing therapeutic challenges—particularly the limited efficacy of conventional treatments and the formidable barrier posed by the BBB.[14] Although AD, PD, HD, and ALS differ in clinical manifestations and pathological mechanisms, they share a common pathological foundation: progressive degeneration and apoptosis of specific neuronal populations, accompanied by aberrant protein aggregation, mitochondrial dysfunction, and chronic neuroinflammation.[50–53] Nanocarrier systems, endowed with excellent biocompatibility, engineering versatility, and superior BBB penetration capabilities, provide unprecedented opportunities for precise modulation of these complex pathological processes.

In recent years, researchers have developed a variety of functionalized nanoplatforms tailored to disease-specific pathologies, enabling the delivery of small-molecule drugs, neurotrophic factors, monoclonal antibodies, siRNAs, and CRISPR/Cas9 therapeutic payloads. For instance, in AD models, targeted nanoparticles delivering anti-Aβ agents or siRNAs have effectively reduced Aβ deposition.[14] In PD, nanocarriers have been applied to regulate α-synuclein aggregation and protect dopaminergic neurons,[25] while in HD and ALS, nanoformulations delivering neurotrophic and anti-inflammatory agents have demonstrated promise in preserving neural function and delaying disease progression.[54–56] These studies in addition to highlight the multifaceted value of nanomedicine across diverse neurodegenerative disorders but also provide essential experimental foundations for mechanistic refinement and clinical translation.

Alzheimer's Disease

Alzheimer's disease is the most prevalent neurodegenerative condition, characterized by hallmark pathological features such as β-amyloid (Aβ) plaque deposition, abnormal tau phosphorylation, dysregulated brain metal ion homeostasis, reduced acetylcholine (ACh) levels, enhanced oxidative stress, chronic neuroinflammation, and synaptic dysfunction.[57] The impermeability of the BBB presents a major limitation for most conventional drugs, severely restricting their therapeutic efficacy. In recent years, nanotechnology-enabled drug delivery systems have been extensively explored in AD treatment, demonstrating potential for multi-targeted intervention and precision therapy.

Nanotherapeutic Strategies Targeting β-Amyloid

Aβ accumulation is regarded as one of the earliest and most central pathogenic events in AD. Its abnormal production and impaired clearance provoke neurotoxic cascades, leading to neuronal apoptosis and cognitive decline.[58] Given that Aβ primarily accumulates in the brain parenchyma, and most conventional agents fail to cross the BBB effectively, developing nanocarriers that specifically target and eliminate Aβ has become a critical therapeutic strategy. These systems typically employ surface modification with anti-Aβ antibodies, peptides, or glycan ligands (eg, RVG peptide) to achieve precise localization of cerebral Aβ plaques.[59,60]

A diverse range of nanoplatforms has been employed to deliver Aβ-interfering agents. Curcumin, a natural inhibitor of Aβ1-42 oligomerization, exhibits potent anti-amyloid activity but suffers from poor water solubility and low bioavailability. Encapsulation in PLGA nanoparticles significantly enhances its brain-targeting efficiency and Aβ-binding affinity.[61] Studies have demonstrated that curcumin-loaded PLGA nanoparticles exhibit pronounced cerebral accumulation, reduce Aβ plaque burden, and improve learning and memory in AD mouse models.[21] To further enhance neuronal delivery, Tet-1 peptide-modified PLGA nanocarriers have been developed. For instance, Mathew et al conjugated curcumin to Tet-1-functionalized

PLGA nanoparticles, improving neuronal uptake and demonstrating antioxidant and anti-Aβ aggregation effects in vitro.[62] More recently, Saleh et al engineered Tet-1-PLGA platforms to deliver small flavonoids like berberine and isoflavones, which alleviated tau pathology and cognitive deficits in AD models.[63,64] These findings validate the efficacy of Tet-1 modification and extend its applicability to diverse therapeutic payloads, paving the way for individualized interventions in neurodegenerative disease.

Donepezil, a widely used AChE inhibitor, has also been incorporated into nanocarrier systems to overcome its pharmacokinetic limitations. Although donepezil enhances cholinergic neurotransmission and alleviates cognitive deficits, its low oral bioavailability, limited brain distribution, and peripheral side effects compromise its therapeutic durability. To address these issues, various nanodelivery systems have been developed to enhance CNS targeting and prolong drug action. For example, Silva et al compared PLA-PEG nanoparticles and exosome-based formulations loaded with donepezil in AD animal models.[65] Exosomes demonstrated superior BBB penetration, brain accumulation, and cognitive improvement. Similarly, Parviz et al designed chitosan-PEG composite nanospheres that significantly enhanced cerebral drug retention and improved behavioral outcomes in AD mice.[66]

Nanoemulsions have also emerged as promising platforms for CNS delivery of donepezil. Studies have demonstrated that donepezil nanoemulsions possess uniform particle size and gastrointestinal stability, with enhanced in vitro drug release compared to standard formulations. In animal models, they exhibited higher peak plasma concentrations (Cmax) and prolonged half-life ($t_1/_2$), suggesting superior pharmacokinetic and brain-targeting properties.[67] Additionally, intranasal delivery has gained attention as a non-invasive route that bypasses first-pass metabolism and exploits the olfactory pathway for direct brain access. Kaur et al developed a nasal nanoemulsion formulation of donepezil, which significantly enhanced brain accumulation and improved learning and memory in AD mice.[68] Together, these findings underscore nanoemulsions as potent platforms for enhancing donepezil solubility, stability, and delivery efficacy, with future research warranted on integrating other delivery routes such as gels and nasal sprays to optimize therapeutic compliance and specificity.

Resveratrol, a natural polyphenol with antioxidant, anti-inflammatory, and anti-Aβ aggregation properties, has attracted considerable attention in AD research. However, its clinical application is hampered by poor solubility, rapid metabolism, and low bioavailability. Nanodelivery platforms have been employed to overcome these limitations and enhance its therapeutic performance. Polymeric nanoparticles, liposomes, nanoemulsions, and solid lipid nanoparticles have all been utilized for resveratrol encapsulation and delivery. For example, Loureiro et al developed solid lipid nanoparticles co-loaded with resveratrol and grape extract, functionalized with OX26 monoclonal antibodies targeting the transferrin receptor to facilitate BBB penetration. This system exhibited strong brain-targeting ability and Aβ inhibition in vitro.[69]

Abbas et al constructed a theranostic platform co-encapsulating resveratrol and SPIONs within chitosan-coated liposomes, enabling magnetic-guided intranasal brain delivery and MRI imaging. This system effectively targeted Aβ-rich regions in AD animal models, enhanced imaging contrast, and demonstrated Aβ plaque clearance and neuroprotection in histopathological assessments.[70] Nanocarriers provide a promising strategy to improve resveratrol's solubility and stability, increase cerebral accumulation, and prolong therapeutic action. Future studies should focus on optimizing targeting efficiency and validating efficacy and safety in large-animal models.

In conclusion, nanocarrier-based therapeutic strategies have demonstrated remarkable advantages in the treatment of Alzheimer's disease—particularly in enhancing Aβ clearance, restoring cholinergic function, and delivering multi-targeted natural products. Future research should emphasize structural optimization, improved brain-targeting precision, and integrated theranostic design. Rigorous evaluation in large-animal models and preclinical studies will be essential to lay the foundation for successful clinical translation.

Combined Nanotherapeutic Strategies Targeting Tau Pathology, Inflammation, and Oxidative Stress

Beyond Aβ deposition, hyperphosphorylation of tau protein and the subsequent formation of neurofibrillary tangles (NFTs) constitute another pivotal pathological hallmark of Alzheimer's disease, closely associated with disease progression. In addition, AD is frequently accompanied by chronic neuroinflammation and heightened oxidative stress, manifested by overactivation of microglia, dysregulated inflammatory cytokine secretion, and elevated levels of ROS.

These pathological processes act synergistically to exacerbate neuronal injury. Accordingly, multi-targeted intervention strategies that concurrently address tau pathology, inflammation, and oxidative stress have become a focal point in AD therapeutic development. Nanocarrier-based delivery systems, with their capacity for co-loading multiple agents, precise targeting, and microenvironment-responsive release, provide an ideal platform for implementing such combinatorial approaches.[71]

In the realm of tau-targeted therapies, studies have reported the use of polyethyleneimine (PEI)-modified liposomes to deliver tau-specific siRNA, resulting in significant reductions in phosphorylated tau expression and cognitive improvement in murine models. For example, Wen et al developed PEG-PEI nanoparticles to deliver siRNA targeting ROCK II, which effectively alleviated cognitive deficits in AD mice, highlighting the potential of this strategy in modulating tau-associated signaling pathways.[72] Furthermore, Wang et al engineered a neuron-targeted nanocomposite capable of systemically delivering BACE1 siRNA, successfully traversing the BBB, reducing cerebral Aβ burden, and improving cognitive function.[73]

In targeting inflammation and oxidative stress, natural polyphenolic compounds such as quercetin, ginkgolide, and rapamycin have garnered significant attention due to their multifunctional properties, including ROS scavenging, inhibition of microglial activation, and regulation of mTOR/NF-κB signaling. Encapsulating these agents into PLGA nanoparticles, nanomicelles, or solid lipid nanoparticles improves their solubility, bioavailability, and enables targeted brain release, thereby amplifying neuroprotective efficacy. Quercetin-loaded PLGA nanoparticles, for instance, significantly extend plasma half-life and reduce cerebral Aβ levels and oxidative stress markers in AD models, ultimately improving cognitive performance.[74] Ginkgolide has similarly demonstrated potent anti-inflammatory and neuroprotective effects by suppressing NF-κB activation.[75]

Rapamycin, owing to its multifaceted role in autophagy modulation, mTOR pathway inhibition, and antioxidant response, has recently emerged as a promising agent in AD therapy. Animal studies have demonstrated that rapamycin-loaded nanocarriers promote Aβ clearance through autophagy activation and ameliorate cognitive deficits.[76] Wang et al further revealed that in a diabetes-induced AD model, rapamycin suppressed the mTOR/p70S6K pathway, reduced both Aβ and phosphorylated tau levels, and improved mitochondrial function.[77] Moreover, Lai et al demonstrated in a zinc-induced tau phosphorylation model that rapamycin simultaneously modulates the mTOR and Nrf2/HO-1 pathways, mitigating oxidative stress and inhibiting aberrant tau phosphorylation, thereby exerting significant neuroprotective effects.[78] Collectively, these findings underscore rapamycin's therapeutic promise through its coordinated regulation of multiple neurodegenerative mechanisms.

In summary, nanocarrier-based systems provide significant advantages in simultaneously targeting tau pathology, neuroinflammation, and oxidative stress. Future investigations should focus on optimizing drug combinations and nanostructured design to enhance delivery efficiency and targeting precision, ultimately advancing multidimensional, precision-based interventions for Alzheimer's disease.

Theranostic Platforms and Future Perspectives

In the treatment of Alzheimer's disease, early diagnosis, targeted drug delivery, and therapeutic monitoring have traditionally existed as disjointed processes, limiting the timeliness and efficacy of precision interventions. In recent years, the concept of theranostics—the integration of diagnostic imaging and therapeutic delivery into a unified nanoplatform—has gained prominence in neurodegenerative disease research. This approach enables real-time visualization of drug biodistribution and treatment response, aligning with the broader goals of precision medicine.[79]

Contemporary theranostic systems are typically constructed using magnetic nanoparticles (eg, Fe_3O_4), quantum dots, near-infrared dyes, or PET imaging probes, co-loaded with therapeutic agents to create dual-functional platforms. These systems in addition to facilitate precise imaging of brain-targeted regions but also incorporate stimulus-responsive drug release mechanisms that enhance therapeutic efficacy. For example, one study reported the development of an Fe_3O_4-based ranibizumab delivery system with robust MRI contrast capabilities. This platform enabled targeted drug release at Aβ-rich sites and significantly improved cognitive function in animal models while enhancing imaging contrast in affected regions.[80]

Although research on theranostic nanoplatforms in AD remains in its infancy, the approach aligns well with the evolving landscape of precision medicine, particularly for chronic neurodegenerative diseases requiring dynamic, long-term management. Future development should focus on enhancing imaging resolution, refining controlled-release mechanisms, and ensuring biosafety and reproducibility in large-scale manufacturing—critical factors for facilitating clinical translation.

Parkinson's Disease

Parkinson's disease is a prevalent neurodegenerative disorder primarily characterized by the selective degeneration of dopaminergic neurons in the substantia nigra pars compacta of the midbrain, leading to a marked reduction in dopamine levels within the striatum and triggering a spectrum of motor dysfunctions.[81] Beyond the classical mechanism of neurotransmitter deficiency, PD pathogenesis involves multifactorial pathological processes, including abnormal aggregation of α-synuclein, neuroinflammatory responses, oxidative stress, and mitochondrial dysfunction.[82,83] Clinically, treatment remains largely dependent on small-molecule drugs such as levodopa (L-DOPA), yet these agents are limited by short half-life, poor BBB permeability, and pronounced peripheral side effects, severely constraining their long-term efficacy and safety.[84] Hence, there is an urgent need to develop more precise, efficient, and brain-targeted drug delivery systems. In recent years, nanomedicine has emerged as a promising avenue for the precision treatment of PD, owing to its controlled-release characteristics and enhanced brain-targeting capacity. The following sections summarize recent advances along three principal therapeutic strategies.

Nanodelivery Optimization of Dopamine Replacement Therapy

The hallmark pathological feature of PD is the progressive degeneration of dopaminergic neurons in the substantia nigra, resulting in a substantial depletion of striatal dopamine and the emergence of classic motor symptoms such as tremors and bradykinesia. Dopamine replacement therapy remains the frontline clinical approach, with principal agents including levodopa, dopamine receptor agonists (eg, pramipexole, ropinirole), and monoamine oxidase-B inhibitors (eg, selegiline). However, these small molecules face multiple therapeutic challenges, including limited BBB permeability, short plasma half-life, and significant peripheral side effects, all of which compromise their long-term utility and patient compliance.[85,86]

Nanocarrier-based delivery systems provide novel solutions for optimizing dopamine replacement therapy. Biodegradable polymeric platforms such as PLGA nanoparticles, when PEGylated, demonstrate enhanced systemic stability and can be further modified with brain-targeting ligands (eg, transferrin, lactoferrin, RVG peptide) to traverse the BBB and accumulate within the striatum. Studies have demonstrated that such surface-modified PLGA nanoparticles effectively deliver levodopa, increase its cerebral bioavailability, prolong therapeutic duration, and mitigate peripheral side effects such as gastrointestinal irritation and hypotension.[14]

Intranasal administration, a non-invasive route bypassing the BBB, allows for direct CNS delivery. Researchers have developed various nanomicelles and nanoparticles capable of delivering dopamine or its precursors via the nasal pathway, significantly enhancing brain drug concentration while reducing systemic exposure and peripheral toxicity.[87] For instance, Tang et al designed nanoparticles co-modified with lactoferrin and borneol, achieving efficient intranasal delivery of dopamine and improving motor performance in PD model rats. This study highlighted the excellent brain-targeting and therapeutic efficacy of lactoferrin-modified nanoparticles administered intranasally.[88]

Inhibition of α-Synuclein Aggregation and Gene Regulation

α-Synuclein (α-syn) is a key pathogenic protein in PD, whose abnormal aggregation into Lewy bodies is considered a principal source of neurotoxicity. Overexpression, structural misfolding, or impaired clearance of α-syn can lead to toxic accumulation, triggering neuroinflammation and dopaminergic neuronal degeneration.[25] In recent years, diverse strategies have been developed to inhibit α-syn aggregation and regulate its expression.

One such strategy involves the use of single-chain variable fragment antibodies (scFvs) to specifically recognize and neutralize α-syn aggregates. Schlichtmann et al engineered scFvs targeting α-syn aggregates and delivered them into PD mouse models via adeno-associated virus (AAV) vectors.[89] The scFvs significantly reduced α-syn expression in the substantia nigra and improved motor functions, underscoring their therapeutic potential in halting PD progression.

Another approach utilizes receptor-mediated transcytosis to deliver biologics across the BBB. Pardridge et al proposed a fusion protein strategy wherein therapeutic antibodies are conjugated to IgGs targeting endogenous receptors such as the insulin or transferrin receptor, facilitating their transcytosis via the RMT pathway.[43] This "molecular Trojan horse" strategy has been successfully employed to transport neurotrophic factors, detoxifying receptors, and therapeutic antibodies into the brain, providing a novel route for PD treatment. Furthermore, lipid nanoparticles (LNPs) modified with receptor-specific IgGs have been developed for the delivery of plasmid DNA encoding therapeutic genes. These LNPs can traverse the BBB through RMT and represent a promising avenue for non-viral gene therapy in PD.

In summary, scFv-mediated blockade of α-syn aggregation effectively reduces neurotoxicity and represents a critical therapeutic strategy. Meanwhile, the RMT-enabled delivery of biologics provides a practical and scalable method for crossing the BBB. Together, these approaches in addition to broaden the therapeutic landscape for PD but also pave the way for targeted intervention at the molecular origins of disease.

Neurotrophic Factor Delivery and Neuroprotection

The progressive loss of dopaminergic neurons in the substantia nigra underlies the motor deficits characteristic of PD. Given the limited regenerative capacity of CNS neurons, neurotrophic factors (NTFs) such as brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), and nerve growth factor (NGF) have emerged as promising agents for neuroprotection and repair.[90–93] These NTFs activate signaling pathways including PI3K/Akt and MAPK/ERK to inhibit neuronal apoptosis, promote axonal regeneration, and sustain synaptic integrity.

However, the clinical application of NTFs is hindered by their large molecular weight, high hydrophilicity, and vulnerability to enzymatic degradation, which prevent them from efficiently crossing the BBB. To address this, researchers have explored a range of nanocarrier-based delivery systems. Zhang's team developed a non-viral, TfR-targeting "Trojan horse" liposomal platform to encapsulate GDNF plasmid DNA, achieving targeted gene delivery to the brain via intravenous injection. This system facilitated receptor-mediated endocytosis of the GDNF vector into the striatum, significantly enhancing local GDNF expression and tyrosine hydroxylase (TH) activity, thereby nearly restoring motor function in PD rats.[94]

Chen et al further advanced this strategy by combining it with ultrasound-targeted microbubble destruction to enhance delivery efficiency. They formulated PEGylated liposomes loaded with GDNF plasmid and conjugated them with microbubbles. Under focused ultrasound, transient BBB permeability was induced, promoting efficient GDNF transfection and expression in the midbrain. This approach significantly improved rotational behavior and motor coordination in PD rats.[95]

In recent years, researchers have developed a variety of innovative nanoplatforms to address the challenges of NTF delivery in PD, aiming to enhance both selectivity and safety. One notable advance is the development of stimulus-responsive nanocarriers. For example, glucose- and trehalose-functionalized polymeric carbon dots (GT-PCDs) exhibit ROS-responsiveness, enabling efficient release of loaded plasmid DNA under oxidative stress conditions. This system significantly increased GDNF expression in the brain and improved motor function and neuroinflammation in PD mouse models.[96] Such multifunctional nanocarriers represent a promising strategy for gene therapy and autophagy modulation in neurodegenerative disease.

Huntington's Disease

Huntington's disease is an autosomal dominant neurodegenerative disorder caused by the expression of a mutant huntingtin-(mHTT) protein. Clinically, it manifests with progressive motor dysfunction, cognitive decline, and psychiatric disturbances.[97] The underlying pathogenesis is multifactorial, involving toxic protein aggregation, transcriptional dysregulation, mitochondrial dysfunction, and neuroinflammation.[98] At present, there is no definitive cure, and available therapies are largely symptomatic, providing limited capacity to slow disease progression. Consequently, molecular strategies aimed at suppressing mHTT expression or eliminating its aggregated products have garnered growing research attention.

Nanodelivery of Gene Expression-Modulating Therapeutics

The persistent expression of mutant huntingtin protein is regarded as the fundamental driver of HD pathogenesis. Gene-silencing strategies such as small interfering RNA (siRNA), antisense oligonucleotides (ASOs), and CRISPR-Cas9 systems can suppress mHTT at the mRNA or DNA level, thereby reducing the production of toxic proteins.[99–101]

However, these macromolecular therapeutics are highly susceptible to enzymatic degradation and face formidable barriers in crossing the BBB, rendering effective delivery systems essential.

To this end, various nanoplatforms have been developed to facilitate efficient mHTT gene silencing. Joshi et al engineered PLGA nanoparticles encapsulating a cocktail of three anti-aggregation peptides—QBP1, NT17, and PGQ_9P^2—surface-modified with Polysorbate 80 to enhance BBB permeability.[102] In R6/2 transgenic HD mice, this system markedly reduced mHTT aggregation in the striatum and significantly improved motor coordination and neuronal morphology, underscoring its therapeutic potential. Additionally, self-assembling β-cyclodextrin-based nanoparticles were developed for siRNA delivery targeting HTT. In vitro, this system effectively downregulated HTT expression in rat striatal cells and primary human HD fibroblasts, while exhibiting low cytotoxicity, suggesting its promise for gene therapy in HD.[103]

These nanocarriers in addition to provide protection and controlled release for nucleic acid therapeutics but also enhance BBB penetration through surface engineering, providing a robust platform for gene-based interventions in HD.

Inhibition and Clearance of Protein Aggregates

In addition to aberrant expression, mHTT is pathologically characterized by the formation of neurotoxic oligomers and inclusion bodies within neurons, leading to profound cellular dysfunction. Therefore, strategies aimed at modulating mHTT conformation or promoting its degradation represent a critical axis in HD therapy. Small-molecule aggregation inhibitors (eg, EGCG), molecular chaperone activators (eg, HSP90 regulators), and autophagy modulators (eg, CMA or mTOR pathway inhibitors) have demonstrated therapeutic efficacy in cellular and animal models.[104–107]

Yet these small molecules frequently suffer from poor solubility, low bioavailability, and limited BBB penetration. Nanodelivery platforms have thus been employed to enhance their stability and brain-targeting capacity. Ehrnhoefer et al demonstrated that EGCG could directly interfere with the misfolding of mHTT, suppress aggregation, and ameliorate toxic phenotypes in cell and Drosophila models.[108] Building on this, Cano et al encapsulated EGCG in PEGylated PLGA nanoparticles, which significantly increased its accumulation in the striatum of 3-nitropropionic acid-induced HD mice, reduced mHTT-associated pathology, and improved motor deficits.[109] This study highlights the feasibility of using nanocarriers to deliver aggregation inhibitors, providing a tangible solution to the pharmacokinetic limitations of traditional small molecules. Looking ahead, the development of multifunctional nanoplatforms with brain-targeting specificity, subcellular localization capabilities, and stimuli-responsive release features holds great promise for the precise modulation of mHTT aggregation and toxicity, thus advancing therapeutic strategies for HD.

Multi-Pathway Synergistic Interventions and Adjunctive Protective Strategies

As a multifaceted neurodegenerative disorder, HD encompasses a complex interplay of genetic mutation, protein aggregation, oxidative stress, mitochondrial dysfunction, energy dysregulation, and neuroinflammation. Given this intricate pathology, single-target approaches—such as merely suppressing mHTT expression or inhibiting aggregation—often fail to yield sustained and substantial therapeutic benefits. Thus, multi-targeted interventions, particularly those enabled by nanotechnology, have emerged as a compelling direction in HD research, providing new opportunities for precision therapy.

One representative approach involves the construction of dual- or multifunctional delivery systems co-delivering gene-silencing molecules alongside neuroprotective agents. For example, Sanchez-Ramos et al developed a chitosan-based nanoparticle system for intranasal delivery of siRNA targeting mHTT. This system in addition to effectively downregulated mHTT expression across multiple brain regions in HD mice but also conferred neuroprotection through the intrinsic immunomodulatory properties of chitosan.[110] Likewise, Zhang et al developed a cyclodextrin-modified nanoplatform with optimized surface functionality to enhance siRNA delivery efficiency into neural cells, achieving potent suppression of mutant HTT expression.[111] The design philosophy of this system emphasized simultaneous optimization of targeting, stability, and cellular uptake, underscoring its strong therapeutic potential and translational viability.

These multifunctional nanodelivery strategies in addition to improve brain-targeted delivery of nucleic acid therapeutics such as siRNA, but also facilitate coordinated intervention across multiple pathological pathways through strategic carrier design. Compared to conventional monotherapies, these composite platforms provide broader applicability and therapeutic depth, providing a viable blueprint for multi-mechanistic HD treatment strategies and laying a foundation for future clinical translation.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis is a progressive motor neuron disease that primarily affects upper and lower motor neurons within the brain and spinal cord, ultimately leading to muscle weakness, respiratory failure, and death. Its pathogenesis is complex and multifactorial, involving abnormal protein mutations (eg, superoxide dismutase 1, SOD1, TDP-43, FUS), excitotoxicity, mitochondrial dysfunction, oxidative stress, and neuroinflammation.[112] Although riluzole and edaravone have been approved for ALS treatment, their therapeutic benefits are limited and insufficient to meaningfully halt disease progression.

In recent years, nanocarrier-based delivery systems have demonstrated therapeutic potential in ALS, particularly in enhancing the delivery of neurotrophic factors, modulating inflammation and oxidative stress, and enabling gene expression regulation. These strategies aim to improve the penetration of macromolecular drugs across the blood–cerebrospinal fluid barrier, increase therapeutic efficacy and tissue specificity, and ultimately delay neurodegeneration.

Nanodelivery Strategies for Neurotrophic Factors

Neurotrophic factors play a crucial role in maintaining motor neuron survival, supporting synaptic function, and promoting neuronal regeneration, making them promising therapeutic candidates for ALS.[113] However, due to their macromolecular nature, they are rapidly degraded or cleared in vivo and face significant challenges in crossing the blood–cerebrospinal fluid barrier, which compromises their therapeutic efficacy via conventional administration routes.[114]

To overcome these limitations, various nanodelivery platforms have been developed to enhance the stability and delivery efficiency of neurotrophic factors. For example, Leyton-Jaimes et al constructed mesoporous silica nanoparticles (MSPs) encapsulating mimetic peptides of CNTF, GDNF, and VEGF, which were directly injected into the cervical spinal cord of SOD1G93A mice. The treatment significantly delayed disease progression, prolonged survival, and improved motor function.[115] Similarly, PEG-PLGA nanoparticles have been employed to deliver BDNF and IGF-1 via the intranasal route in ALS models, achieving enhanced accumulation in the brain, improved neuronal survival, and ameliorated motor deficits.[116] These findings indicate that nanocarriers in addition to stabilize neurotrophic factors in vivo but also enable their targeted delivery across the blood–CSF barrier, thereby improving their clinical applicability.

Strategies for Inflammation and Oxidative Stress Modulation

Neuroinflammation and oxidative stress are pivotal contributors to motor neuron degeneration in ALS. Inflammatory processes are marked by microglial activation and pro-inflammatory cytokine release, while oxidative stress involves the accumulation of ROS, leading to mitochondrial impairment and lipid peroxidation.[117] Anti-inflammatory and antioxidant therapies have thus become focal points in ALS research.

Nanodelivery systems have proven advantageous in enhancing the bioavailability of ALS therapeutics. Edaravone, a free radical scavenger, exerts neuroprotective effects by mitigating oxidative damage to motor neurons. Its mechanism involves the clearance of excess ROS, thereby decelerating neurodegeneration. For instance, Ferreira et al developed a polymeric nanoparticle system to encapsulate edaravone for sustained and stable release.[118] This platform enhanced edaravone's CNS penetration, increased its accumulation in brain tissues, and bolstered its antioxidant activity, significantly reducing ROS-induced neuronal damage. In both in vitro and animal models of ALS, the nanoformulation demonstrated superior neuroprotective efficacy compared to free drug, indicating its promise in delaying disease progression. Additionally, Medina and colleagues developed a PLA-PEG nanoparticle system encapsulating the RARβ agonist adapalene. Following intravenous administration in SOD1G93A mice, the nanoparticles successfully delivered adapalene to the CNS, activated retinoic acid signaling, and improved motor performance, neuronal survival, and lifespan.[119]

Collectively, these studies demonstrate that nanodelivery systems provide novel therapeutic avenues for ALS by improving drug stability, targeting efficiency, and CNS bioavailability. The use of edaravone and adapalene within nanoformulations in addition to enhances local drug concentrations in diseased regions but also achieves superior neuroprotection compared to conventional formulations. Future research focused on integrating multifunctional nanocarriers with mechanistic precision interventions may further accelerate the clinical translation of ALS therapeutics.

Targeting Pathogenic Genes and RNA Interference Strategies

Over 10% of ALS cases are familial (fALS), commonly associated with mutations in genes such as SOD1, C9orf72, TDP-43, and FUS.[120–122] RNA-based therapeutic strategies, including siRNAs, ASOs, and CRISPR/Cas9 systems, have been extensively investigated for their potential to silence these pathogenic genes. However, challenges such as poor in vivo stability, nuclease susceptibility, and limited BBB permeability have severely hindered their clinical translation.

To address these issues, nanocarriers have been widely employed for the precise delivery of RNA therapeutics, providing protection from degradation and facilitating BBB penetration. Moeller et al designed a core–shell mesoporous silica nanoparticle (MSN) platform equipped with multifunctional polymeric caps for siRNA delivery. The system achieved high siRNA loading via electrostatic interactions and enabled efficient intracellular release, significantly enhancing gene silencing efficacy. In vitro experiments demonstrated up to 90% gene knockdown at low doses, confirming its excellent delivery performance and biocompatibility.[123]

These findings illustrate that nanocarriers provide considerable advantages in protecting RNA therapeutics, enhancing their enrichment in target tissues, and enabling multi-target interventions. As such, they have become indispensable tools in the advancement of precision therapeutics for ALS.

Figure 2 illustrates the core pathological mechanisms of multiple neurodegenerative diseases—Alzheimer's disease, Parkinson's disease, Huntington's disease, and ALS—alongside mainstream nanodelivery strategies and their therapeutic

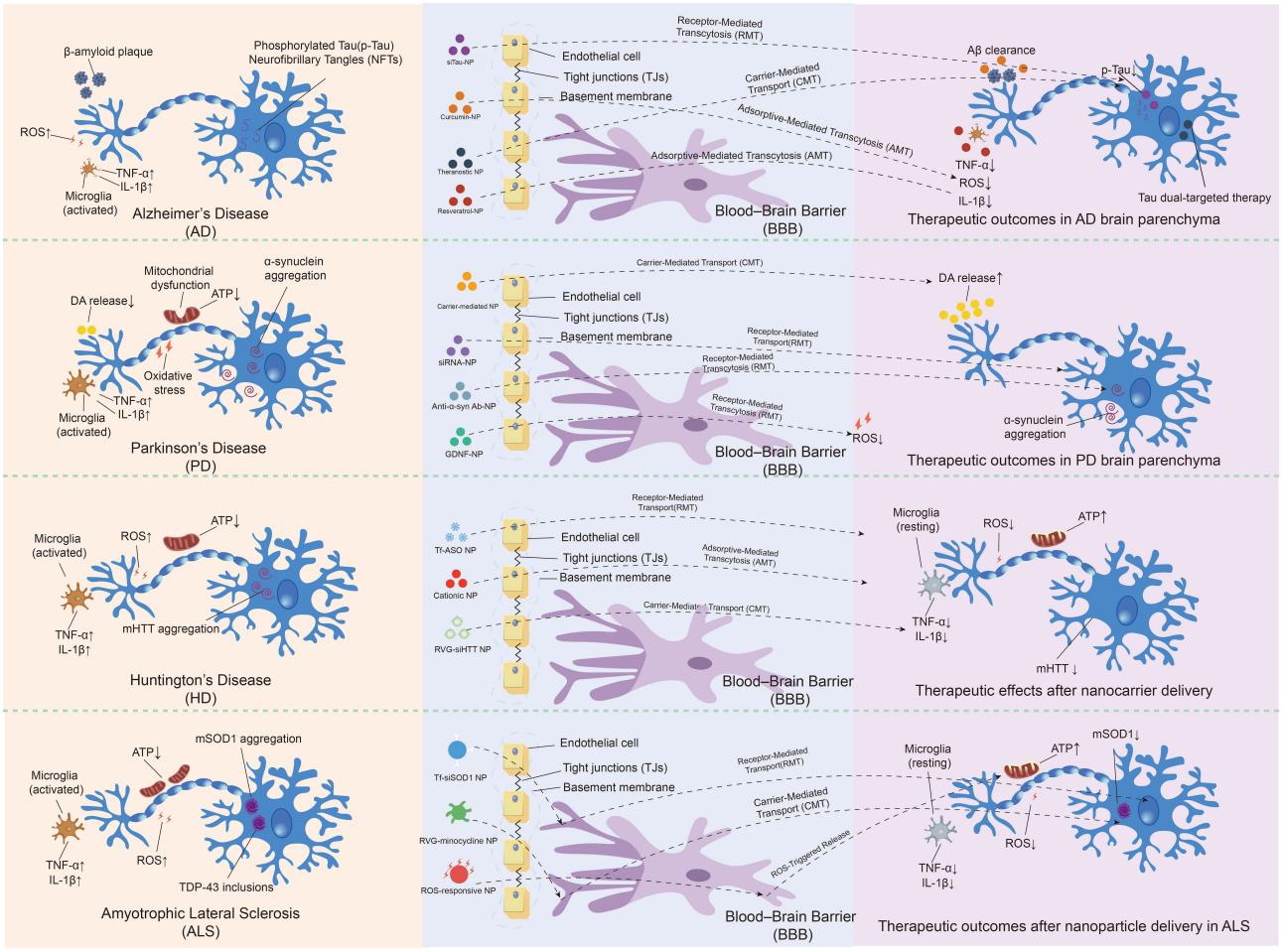

Figure 2 Schematic Representation of BBB-Crossing Mechanisms and Therapeutic Outcomes of Nanocarriers in Neurodegenerative Diseases. Representative mechanisms and therapeutic outcomes of nanoparticle delivery in Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) are shown. Nanocarriers cross the blood–brain barrier (BBB) via adsorptive-mediated transcytosis (AMT), carrier-mediated transport (CMT), or receptor-mediated transcytosis (RMT), delivering therapeutic agents (eg, siRNA, antibodies, neurotrophic factors) to diseased brain regions and improving pathological outcomes. Arrow indicators: → (all dashed arrows): Direction of action or effect. ↑ (upward arrow): Increase or activation. ↓ (downward arrow): Decrease or inhibition.

targets and effects in the brain. This comprehensive visual aids in understanding both the shared and distinct mechanisms of nanocarrier actions across different disorders.

Given the complex etiology of neurodegenerative diseases, the dispersed nature of drug targets, and the formidable challenge of BBB penetration, effective therapeutic options remain scarce. Nanotechnology has demonstrated promise by enhancing drug stability, improving pharmacokinetics, and facilitating BBB transit, contributing to delayed neuronal degeneration and improved neural function. To date, nanocarriers have been broadly employed to deliver a range of therapeutic agents—including small molecules, proteins, nucleic acids, and neurotrophic factors—demonstrating beneficial effects in mitigating pathological protein aggregation, reducing neuroinflammation, and repairing neuronal damage. Various nanoplatforms—such as polymeric nanoparticles, liposomes, nanomicelles, and biomimetic systems—have been designed to accommodate diverse disease conditions, with several demonstrating promising efficacy in preclinical animal models. While most research remains at the preclinical stage, ample evidence suggests that nanotechnology may open a transformative therapeutic avenue for neurodegenerative disorders and serve as a powerful complement to conventional approaches.

Smart and Organelle-Targeting Nanocarrier Systems

Stimuli-Responsive Nanocarriers

The pathological regions of neurodegenerative diseases are often characterized by distinct microenvironmental changes, such as acidic pH, elevated ROS levels, and abnormal expression of specific enzymes (eg, esterases, proteases).[124–126] These features provide a biological foundation and activation mechanism for designing stimuli-responsive nanocarriers with site-specific drug release capabilities.

Stimuli-responsive nanocarriers are engineered platforms capable of releasing therapeutic agents in response to specific pathological stimuli, demonstrating high spatial precision and temporal control.[127] Compared with conventional delivery systems, these platforms enable precise on-site drug release within diseased tissues, significantly enhancing targeting efficiency and local therapeutic effects while minimizing systemic toxicity. In the treatment of neurodegenerative diseases, such systems have demonstrated considerable promise, particularly in improving central drug delivery efficiency, achieving on-demand release, and reducing systemic exposure.

pH-Responsive Nanocarriers

Among intelligent delivery strategies, pH-responsive systems are among the most extensively developed. Their design capitalizes on the acidic features of pathological or intracellular environments—such as lysosomes, endosomes, and activated microglia—to trigger carrier disassembly or swelling, thereby achieving precise drug release at the site of action.[128] These systems effectively identify acidic conditions, increasing drug concentrations in lesions while reducing toxicity to healthy tissues and improving central nervous system drug delivery. Intracellular structures such as lysosomes and endosomes typically present an acidic milieu (pH ~4.5–5.5), and activated microglia and diseased regions also often exhibit localized acidification (pH ~6.5–6.8), providing a physiological basis for pH-triggered release mechanisms.[129]

A critical aspect in the construction of such systems lies in balancing chemical stability with acid-sensitivity. Common strategies involve introducing hydrazone, Schiff base, or acid-labile ester bonds that hydrolyze in acidic environments, triggering drug release.[130] Additionally, polyelectrolytes such as polyacrylic acid exhibit excellent conformational responsiveness and mucoadhesive properties under acidic conditions, enhancing drug retention and penetration in the nervous system. Related studies have demonstrated that polyacrylic-acid-based nanocarriers significantly improved brain drug accumulation and therapeutic outcomes in Alzheimer's disease mouse models.[131]

In an experimental study, Gisbert-Garzarán et al designed a pH-responsive mesoporous carbon nanoparticle system that efficiently released drugs at lysosomal pH (pH 5.0) while remaining stable at physiological pH, thereby significantly enhancing intracellular targeting efficiency.[132] Although the model in the present study was not specific to neurological diseases, the design concept holds broad translational relevance for CNS-targeted delivery.

In summary, pH-responsive platforms dynamically respond to pathological microenvironments, enabling precise "site-specific" drug release within cellular compartments or diseased tissues. They demonstrate substantial potential for enhancing efficacy and minimizing adverse effects. Future development may focus on combining pH-responsive systems with brain-targeting ligands and ROS-responsive mechanisms to improve CNS delivery specificity and accuracy.

ROS-Responsive Nanocarriers

Reactive oxygen species play a pivotal role in the pathogenesis of numerous neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease. Abnormally elevated ROS levels arise from mitochondrial dysfunction, misfolded protein-induced stress, and microglial hyperactivation.[133] Excess ROS induces lipid peroxidation, DNA damage, and protein modifications, activates inflammatory cascades, and triggers neuronal apoptosis—key drivers of disease progression.[134]

To address this, researchers have developed ROS-responsive nanocarriers utilizing sulfur, selenium, boronate, or thioether oxidation-sensitive linkers to enable selective drug release in high ROS environments. These systems remain stable under normal physiological conditions but rapidly disassemble in pathological sites, maximizing therapeutic efficacy while reducing exposure to healthy tissues and enhancing lesion-specific targeting.[135]

Several studies have confirmed the efficacy of ROS-responsive systems in PD models. Lei et al developed polydopamine-based curcumin-loaded nanoparticles (pDA-Cur NPs), which released curcumin in response to ROS, reduced ROS levels, inhibited α-synuclein aggregation, and improved motor function and nigral neuron survival in PD mice.[136] Another study employed graphene quantum dots capable of crossing the blood–brain barrier and inhibiting α-synuclein aggregation, alleviating striatal damage and improving behavioral outcomes in PD mice, highlighting their neuroprotective potential.[137]

Collectively, ROS-responsive platforms provide powerful mechanisms for targeted drug release and neuroprotection in neurodegenerative disease models. Their ability to enhance local drug concentrations while reducing systemic side effects makes them promising candidates for clinical translation. Future work may integrate other stimuli and targeting moieties to further enhance multifunctionality and clinical applicability.

Enzyme-Responsive Nanocarriers

Neurodegenerative diseases are often accompanied by inflammatory responses and proteostasis disruption, leading to upregulation of various enzymes such as matrix metalloproteinases (MMPs), lysosomal enzymes (eg, Cathepsin B/D), and acetylcholinesterase (AChE).[138–140] These enzymes are critically involved in inflammation regulation, phagocytosis, autophagy, and pathological protein degradation, making them ideal "pathological microenvironmental triggers" for designing enzyme-responsive delivery systems.

The core strategy involves incorporating enzyme-cleavable peptides or chemical bonds into nanocarriers, which are selectively recognized and cleaved by target enzymes such as AChE, MMPs, or Cathepsin B. Upon entering the lesion site, enzyme-mediated cleavage initiates carrier disassembly and precise drug release. For instance, in AD models, AChE-responsive mesoporous silica systems with polyglutamic acid gates demonstrated efficient site-specific release, confirming their spatial selectivity and release efficiency.[141] Si et al reported elevated MMP-9 expression in MPTP and A53T mouse models, which impaired AQP4 polarization and brain lymphatic flow. Inhibition of MMP-9 restored AQP4 polarity, improved lymphatic clearance, and protected dopaminergic neurons, highlighting MMP-9 as a valid therapeutic target and trigger for enzyme-responsive systems.[138]

In AD, AChE is in addition to a key enzyme in ACh hydrolysis but also facilitates Aβ aggregation, forming neurotoxic AChE-Aβ complexes that accelerate plaque formation and neurotoxicity.[142–144] These complexes induce oxidative stress, mitochondrial dysfunction, and inflammation, ultimately exacerbating neuronal apoptosis.[145] Bartolini et al further demonstrated AChE's interaction with phosphorylated tau (p-Tau), promoting neurofibrillary tangle formation and aggravating neuropathology.[146]

Other proteases, such as Cathepsin B/D and Asparagine Endopeptidase (AEP), also play vital roles in disease pathology, including autophagy imbalance and pathogenic protein processing. In lysosomal dysfunction settings, Cathepsin B can cleave APP, promoting Aβ generation and plaque formation under pathological conditions, though it may also facilitate Aβ clearance depending on enzymatic activity and local context.[147–151] Cathepsin D, a major lysosomal aspartyl protease, is involved in α-synuclein degradation, and its dysfunction contributes to toxic protein accumulation and neurodegeneration in PD.[152]

Given their lesion-specific expression and substrate specificity, Cathepsin-responsive systems have been developed using sensitive peptide linkers for lysosomal targeting and precise drug release in diseased environments. These platforms enhance targeting accuracy while minimizing off-target toxicity.

AEP, also known as δ-secretase, has recently emerged as a pivotal lysosomal cysteine protease in both AD and PD pathologies.[153,154] Activated by acidic lysosomal pH and inflammatory mediators such as C/EBPβ, AEP cleaves APP and Tau into highly aggregation-prone fragments, promoting plaque and tangle formation in AD.[155,156] In PD models, AEP cleaves α-synuclein into toxic fragments, facilitating Lewy body formation and neuronal damage.[157,158] Notably, AEP expression is markedly upregulated during the early stages of disease and is regulated by inflammation and oxidative signaling pathways, exhibiting a distinct lesion-specific activation profile.[159] This makes AEP an ideal trigger for enzyme-responsive drug delivery systems. Nanocarriers incorporating AEP-recognition motifs (eg, Asn–X) have shown promising results in selectively disassembling and releasing drugs within AEP-enriched regions, demonstrating therapeutic efficacy in preclinical models.[160]

In conclusion, stimuli-responsive nanocarriers that sense pathological microenvironmental signals characteristic of neurodegenerative diseases provide powerful strategies for precise drug delivery. pH-responsive systems leverage the acidic nature of lysosomes and inflammatory regions, facilitating intracellular and microglial targeting. ROS-responsive platforms align with oxidative-stress-driven pathogenesis, particularly in AD and PD models. Enzyme-responsive carriers target overexpressed proteases to intervene in inflammation and protein aggregation with high specificity. Emerging dual- and multi-responsive systems further enhance targeting precision, although design complexity and clinical translation hurdles remain challenges to be addressed.

Organelle-Targeting Nanocarrier Systems

In neurodegenerative diseases, cellular dysfunction often originates from damage to specific subcellular organelles such as mitochondria, lysosomes, and nuclei. The pathological disruption of these structures in addition to initiates neurotoxic cascades but also accelerates the widespread progression of disease. Accordingly, achieving precise drug delivery at the subcellular level has emerged as a key strategy for enhancing both therapeutic efficacy and targeting specificity. In recent years, advances in nanotechnology have made organelle-targeted delivery increasingly feasible, enabling the transport of antioxidants, neurotrophic factors, and gene-editing tools directly to sites of pathology, thereby promoting a paradigm shift from "cellular-level" to "organelle-level" precision therapies.[161]

Take mitochondria, for example—these organelles are central to oxidative phosphorylation, ATP production, and ROS generation, and their dysfunction plays a pivotal role in the pathogenesis of AD, PD, and ALS.[162] In both AD and PD, depolarization of mitochondrial membrane potential, disruption of respiratory chain complexes, and excessive ROS production are considered major drivers of neuronal degeneration.[163]

To achieve mitochondrial-specific therapy, researchers have developed active targeting strategies based on mitochondrial membrane potential differences. Among them, the lipophilic cation triphenylphosphonium (TPP) is most widely used. TPP-modified nanoparticles can exploit the negative inner mitochondrial membrane potential to achieve effective accumulation and elevate local drug concentrations.[164] For instance, Zhang et al designed a TPP-functionalized nanovesicle system encapsulating ursodeoxycholic acid (UDCA), which demonstrated remarkable efficacy in a PD mouse model. This system was capable of crossing the blood–brain barrier and specifically localizing to mitochondria in striatal neurons, significantly reducing ROS accumulation, increasing ATP levels by approximately 42.6%, and markedly improving both motor coordination and mitochondrial function.[165]

Moreover, studies have demonstrated that TPP-modified platforms can restore mitochondrial respiratory chain activity, regulate membrane potential, and ameliorate oxidative stress and metabolic imbalance in models of AD and PD. Compared with non-targeted systems, TPP-modified nanoparticles exhibit superior targeting and drug-release efficiency, enabling reduced therapeutic doses and attenuated systemic toxicity.[166,167] A recent study developed a TPP-functionalized MoS_2 nanocomposite system with catalase and superoxide dismutase mimetic activities, which effectively scavenged ROS in AD models. By modulating microglial polarization from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype, this system alleviated neuroinflammation and provided neuroprotection, further demonstrating the broad adaptability of mitochondrial targeting strategies in various neuropathological contexts.[168] In parallel, additional research has explored the encapsulation of coenzyme NAD^+, antioxidant enzymes, and mitochondrial biogenesis-promoting molecules within TPP-modified platforms to achieve multi-pathway synergistic interventions. These approaches in addition to enhance cellular energy supply but also interrupt mitochondrial-mediated apoptotic signaling, thereby amplifying neuroprotective outcomes.[164,165]

In addition to mitochondria, lysosomes—central to autophagy and macromolecular degradation—also play vital roles in neurodegeneration. The accumulation of pathological proteins such as Aβ in AD and mHTT in HD has been closely linked to impaired lysosomal function.[166,169] Encouraging experimental results have emerged from nanocarrier-based strategies aimed at restoring lysosomal integrity and promoting the clearance of protein aggregates.

In one study, researchers administered epigallocatechin gallate nanoparticles (nano-EGCG) to aluminum-induced AD rats. Nano-EGCG significantly enhanced the brain bioavailability of EGCG, restored lysosomal acidification, reduced plaque and neurofibrillary tangle formation, and improved cognitive performance in the Morris water maze.[167] Another study in APP/PS1 transgenic AD mice developed a dual-drug nanoplatform co-delivering EGCG and ascorbic acid (EGCG/AA NPs) using a PEG-PLGA carrier, which enhanced the stability and sustained release of EGCG in brain tissue. This system notably reduced Aβ deposition and neuroinflammation, increased synaptic protein expression, and ultimately improved cognitive function.[170]

These pH-triggered, lysosome-targeted nanoplatforms in addition to improved drug delivery efficiency and bioavailability in the brain but also effectively restored the lysosome-autophagy axis, facilitating the clearance of pathological proteins such as Aβ and phosphorylated tau. Behavioral and histopathological analyses confirmed the therapeutic benefits, reinforcing the promise of lysosomal targeting strategies for neurodegenerative disease treatment.

Beyond mitochondria and lysosomes, other subcellular organelles such as nuclei and autophagosomes are also emerging as precision therapeutic targets. In ALS, where SOD1 mutations are prevalent, researchers have developed adeno-associated virus nanocarriers bearing nuclear localization signals (NLS) to deliver CRISPR-Cas9 components into motor neuron nuclei for base editing or knockout of mutant G93A-SOD1, thereby delaying disease progression. In a study by Lim et al, a split base editor delivered via AAV successfully corrected the SOD1 mutation in ALS mice, significantly improving motor function and extending survival.[171] Wu et al further used CRISPR-Cas9 to knock out mutant SOD1, observing a marked reduction in spinal cord mutant protein expression, evident neuroprotection, and an approximately 25% increase in lifespan relative to controls.[172]

Preliminary studies in HD models have also demonstrated that autophagosome-targeting nanotechnologies can promote the clearance of mHTT. For example, $MnFe_2O_4$ nanoparticles have been demonstrated to enhance mHTT degradation in cells and mouse models, significantly reducing neurotoxicity and underscoring their potential in modulating protein aggregation and autophagic flux.[173]

It is worth noting, however, that despite the clear therapeutic advantages of organelle-targeted nanocarrier systems, numerous challenges impede their clinical translation. Variations in organelle structure, membrane potential gradients, and permeability among different neuronal subtypes may compromise targeting universality. Intracellular trafficking and suborganelle localization may also be confounded by nonspecific degradation and off-target release. Additionally, most current studies are limited to in vitro or small animal models, lacking comprehensive pharmacokinetic, biodistribution, and long-term toxicology evaluations.

To visually illustrate the key strategies and limitations of organelle-targeted nanocarriers, Figure 3 summarizes the major biological barriers, representative targeting mechanisms (eg, membrane potential-driven, pH-triggered, or nuclear signal-mediated), and application pathways of various nanoplatforms directed toward organelles such as mitochondria, lysosomes, autophagosomes, and nuclei. This schematic helps clarify the current landscape and optimization directions of subcellular targeting strategies.

In summary, organelle-targeting nanocarrier systems significantly enhance therapeutic precision and biological efficacy by enabling localized drug delivery to key pathological structures within cells. They represent a critical breakthrough in deep-targeted intervention for neurodegenerative diseases. In the future, advances in high-throughput pathological target identification, membrane permeability modulation, and programmable release design, coupled with systematic pharmacological and toxicological validation, are expected to facilitate the translational journey of these platforms from bench to bedside.

Gene Therapy and Theranostic Platforms

Gene Delivery Systems

A substantial proportion of pathological alterations in neurodegenerative diseases can be attributed to specific genetic abnormalities, such as the overexpression of α-synuclein in PD, SOD1 mutations in ALS, and dysregulated expression of

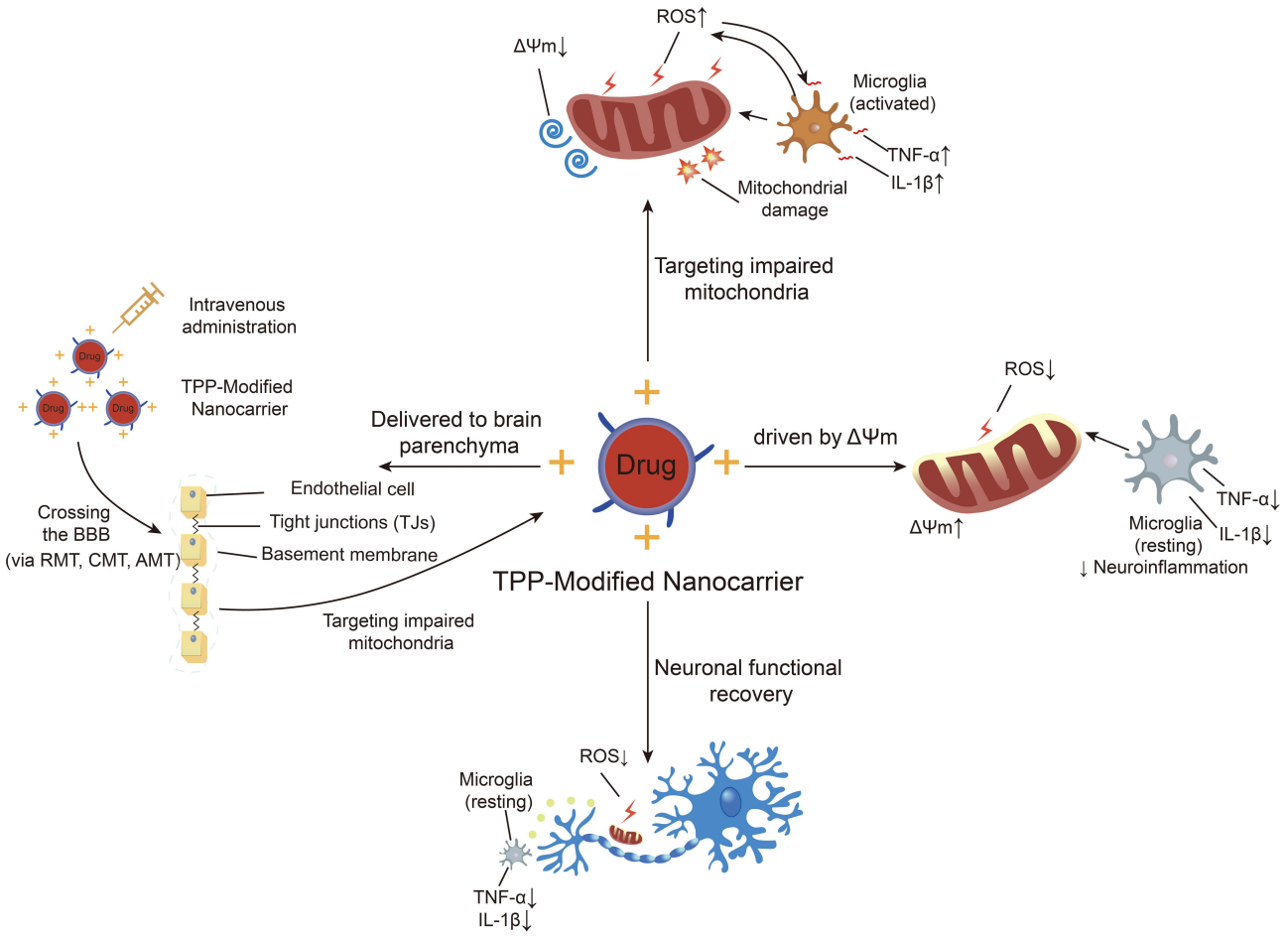

Figure 3 Schematic representation of the mechanism by which TPP-modified nanocarriers target mitochondria. After intravenous administration, the nanocarriers cross the blood–brain barrier via RMT/CMT/AMT mechanisms. Driven by the mitochondrial membrane potential (ΔΨm), they accumulate in damaged mitochondria, releasing their therapeutic payload to reduce ROS, restore mitochondrial function, suppress microglial activation, and ultimately restore neuronal functionality. Arrow indicators: → (all arrows): Direction of action or effect. ↑ (upward arrow): Increase or activation. ↓ (downward arrow): Decrease or inhibition.

mHTT in HD. To target these genetic aberrations, modalities including small interfering RNA (siRNA), antisense oligonucleotides (ASO), messenger RNA vectors, and CRISPR-Cas9-based gene editing systems have been widely explored in recent years as therapeutic strategies.[171,174–176] However, given the intrinsic instability of these nucleic acid agents in vivo, their susceptibility to enzymatic degradation, limited ability to traverse the blood-brain barrier, and low uptake efficiency, nanocarrier-based delivery systems have emerged as essential structural platforms to overcome these bottlenecks. Representative platforms include cationic liposomes (eg, LNPs), polymeric nanoparticles (such as PEI and PEG-PLGA), hybrid nanocarriers, and proteinaceous capsules, often combined with targeting ligands like RVG peptides, transferrin (Tf), or ApoE, as well as pH- or enzyme-responsive designs to achieve high-efficiency delivery to neurons and other cells.

In ALS research, AAV-mediated delivery of siRNA or miRNA has been utilized to suppress mutant SOD1 expression. For example, a research group developed an AAV-miRSOD1 system administered via lingual and intrathoracic injection in SOD1G93A mice, which significantly downregulated SOD1 expression in the spinal cord and respiratory muscles, delayed motor decline by approximately 50 days, preserved neuromuscular junction integrity, and effectively postponed disease endpoints.[177] In PD models, siRNA targeting α-synuclein delivered via RVG-modified polymeric or lipid nanoparticles successfully enhanced brain delivery and reduced protein aggregation, exemplifying the efficacy of RVG-based targeting in CNS RNA therapies.[178] Furthermore, in the realm of CRISPR-mediated gene editing, AAV9-CasRx/HTT gRNA systems enabled precise knockdown of mHTT RNA in HD knock-in pig models, markedly reducing mutant protein levels and restoring neuronal function, thereby underscoring the effectiveness and clinical promise of subnuclear gene editing strategies.[179]

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Collectively, gene delivery platforms that integrate nanomaterials with molecular biology tools provide robust technological support for precise intervention in a range of pathogenic genes implicated in neurodegenerative disorders. Whether through RNA interference, mRNA expression, or CRISPR-based genome editing, these therapies rely on efficient and safe vectors for targeted delivery. While current studies have demonstrated promising outcomes across various animal models, clinical translation still faces challenges such as tissue specificity, off-target effects, and long-term safety. Future research will likely focus on optimizing carrier materials, enhancing BBB penetration efficiency, and developing individualized treatment strategies as the field's core directions.

Theranostic Nanocarriers

In the treatment of neurodegenerative disorders, theranostic nanocarriers—nanoplatforms integrating both diagnostic and therapeutic functionalities—are rapidly emerging as powerful tools for precision intervention. These systems typically co-encapsulate imaging probes and therapeutic agents within a single nanostructure and leverage disease microenvironment-specific triggers (eg, acidic pH, oxidative stress, or enzyme activity) or surface biomarker recognition to achieve localized drug release synchronized with imaging signal output. For instance, in AD models, researchers have constructed magnetic Fe_3O_4 nanoparticle-based systems functionalized with anti-Aβ antibodies and anti-inflammatory agents, enhancing MRI contrast and modulating plaque-associated inflammation to improve cognitive outcomes.[79] Similarly, Shojaei et al developed a 64Cu-labeled TREM2 antibody nanoplatform for PET imaging of microglial activation, enabling early detection of neuroinflammatory states;[180] while THK-565, a near-infrared II probe, allows for high-resolution visualization of deep-brain plaques.[181] To enhance synergistic functionality, current nanocarriers often employ liposomes, polymeric nanoparticles, metal-organic frameworks (MOFs), or hybrid architectures, aiming to optimize signal intensity, drug stability, and targeting efficiency.[182] Such integrated systems have demonstrated closed-loop control capabilities—from lesion identification to therapeutic feedback—in models of AD, PD, and HD, providing highly modular, controllable, and visualized intervention platforms that are shaping the future of theranostic approaches in neurological diseases.

Moreover, a growing number of studies are incorporating smart response mechanisms into theranostic nanocarriers to improve the selectivity and timing of drug release. These systems typically harness specific pathological features of the disease microenvironment as triggering signals for precise drug deployment. Typical mechanisms include oxidative stress response, pH-sensitivity, and enzyme activation. For example, ROS-responsive carriers can detect elevated oxidative stress in AD lesions and release antioxidants locally, effectively scavenging reactive oxygen species and mitigating neural injury. Yuan et al developed a Ru-based nanoplatform with diselenide bonds that, via this mechanism, significantly alleviated neuroinflammation and cognitive deficits in AD models.[183] Similarly, Yang et al designed a dual pH/ROS-responsive nanoplatform co-delivering BACE1-siRNA and rapamycin, intranasally administered in AD mice, which simultaneously suppressed β-secretase expression and improved cognitive behavior.[184] These responsive designs enhance local drug bioavailability while minimizing off-target toxicity, representing a key strategy for clinical translation of theranostic systems.

Looking ahead, the construction of smart closed-loop systems integrating multimodal imaging (eg, PET/MRI, NIR-II/MRI) with multifunctional therapies (including drug release, gene modulation, and immune regulation) is a promising frontier. Such platforms have made substantial progress in synchronizing imaging output with therapeutic feedback, and the integration of AI and machine learning further supports automated treatment decision-making based on real-time imaging data.[185] Regarding BBB traversal, membrane-derived hybrid carriers—such as exosome- and cell membrane-coated nanoparticles—as well as RVG/TGN-modified systems, have significantly improved brain-targeting efficiency in AD and PD models, providing cutting-edge technological support for the precise delivery of nucleic acids, proteins, and small molecules.[186] As illustrated in Figure 4, these platforms enable simultaneous imaging (via MRI/PET) and therapeutic delivery, while the efficacy of neuroprotection can be validated through immunohistochemical analyses (eg, Iba-1, TNF-α), forming a complete closed-loop pipeline from imaging to pathological confirmation.

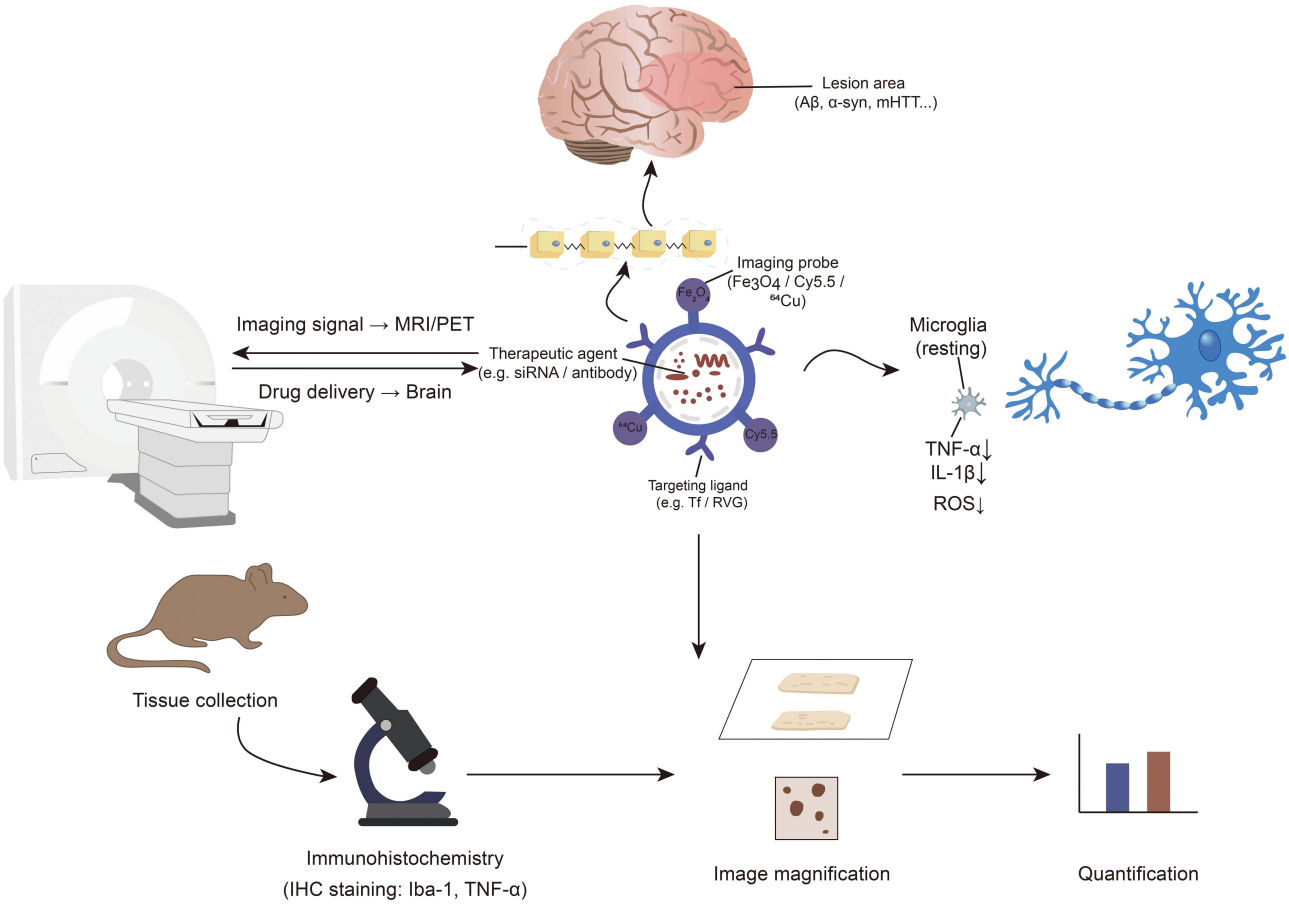

Figure 4 Schematic Illustration of the Mechanism of Theranostic Nanocarriers in Neurodegenerative Diseases. The nanocarrier is functionalized with imaging probes (Fe_3O_4 / Cy5.5 / ^{64}Cu) and targeting ligands (eg, Tf or RVG peptide), enabling MRI/PET imaging and delivery of therapeutic agents (eg, siRNA or antibody) to lesion areas containing Aβ, α-syn, or mHTT. Therapeutic effects include reduced microglial activation and decreased pro-inflammatory factors (TNF-α↓, IL-1β↓, ROS↓), leading to restored neuronal function. Experimental validation involves tissue collection, immunohistochemistry (Iba-1, TNF-α), image magnification, and quantification. Arrow indicators: → (all arrows): Direction of action or effect. ↓ (downward arrow): Decrease or inhibition.

Biosafety and Clinical Translation Challenges of Nanomedicine Systems

Biosafety of Nanomedicine Systems

Inorganic nanomaterials—such as AuNPs, silver nanoparticles (AgNPs), silica nanoparticles, and iron oxide nanoparticles—are often classified as carriers with the highest risk of chronic tissue accumulation and long-term toxicity due to their structural stability and resistance to degradation. Multiple studies have demonstrated that, following injection, these particles rapidly accumulate in the liver and spleen, remain there for prolonged periods, and may also distribute to the lungs, kidneys, muscles, and even the brain.[187]

For instance, 20 nm AuNPs coated with bovine serum albumin exhibited a striking biodistribution pattern in mice: approximately 41% of the injected AuNPs accumulated in the liver and 1.3% in the spleen on the first day. Over time, hepatic AuNP content gradually declined to around 25% by day 120, whereas splenic levels rose. Histological and molecular analyses revealed that long-term retention of AuNPs elevated the expression of inflammation-related markers (Tnfα, Cxcl2) and induced early signs of fibrosis. These findings highlight the poor clearance efficiency of AuNPs in vivo, their complex kinetics of tissue migration and re-aggregation, and their latent risk of chronic toxicity. Consequently, even AuNPs, often regarded as relatively biocompatible, require rigorous evaluation of their long-term in vivo behavior and safety.[188]

Comparative studies have further characterized the in vivo distribution and toxicological profiles of AgNPs and AuNPs following repeated intravenous administration. Yang et al reported that both nanoparticle types predominantly

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localized to reticuloendothelial system (RES) organs such as the liver and spleen; however, AgNPs exhibited markedly higher accumulation in the lungs, kidneys, and heart, and showed greater levels in blood and feces, implying broader systemic distribution and a higher risk of systemic toxicity.[189]

Takeuchi et al compared the biodistribution of bare AuNPs and polyethylene glycol (PEG)-modified AuNPs (20–-30 nm and 50 nm) in mice.[190] PEGylation significantly reduced initial liver and spleen enrichment and prolonged circulation time. Notably, PEG-AuNPs exhibited higher brain accumulation than their unmodified counterparts, indicating an enhanced ability to cross the BBB.

Similarly, Daems et al investigated the pharmacokinetics, tissue distribution, and toxicity of antibody-conjugated AuNPs (Cetuximab-AuNPs) in healthy mice.[191] These functionalized nanoparticles were rapidly cleared from the bloodstream, preferentially accumulated in the liver and spleen, and remained long-term. Short-term studies detected mild hepatic injury and inflammatory responses via biochemical markers, although gross tissue morphology remained largely normal within four weeks. At six months, however, mice displayed renal tubular casts, increased splenic apoptosis, and occasional pulmonary immune-cell infiltration, underscoring the non-negligible risk of delayed toxicity.

Collectively, these studies indicate that, despite surface functionalization or engineering, noble metal nanoparticles continue to preferentially accumulate in the liver and spleen with long-term retention, potentially impacting the kidneys and lungs. AgNPs, in particular, demonstrate broader systemic distribution and stronger toxicity. While PEGylation and antibody conjugation can improve targeting and circulation, they do not eliminate the hazards of bioaccumulation and chronic toxicity.

Immunogenicity and Inflammatory Responses of Nanomedicine Systems

While nanocarriers enhance drug delivery efficiency and prolong blood circulation, they may also trigger host immune activation and inflammatory responses. Both metallic nanoparticles (eg, AuNPs, AgNPs) and organic platforms (eg, PEG-modified nanocarriers) have demonstrated varying degrees of immunogenicity and pro-inflammatory potential in animal studies.

Spherical AuNPs, for example, display measurable immunogenicity and pro-inflammatory activity in murine models.[192] Following intravenous administration, AuNPs predominantly accumulate in the liver and spleen, induce elevated levels of inflammatory cytokines (TNF-α, IL-1β, IL-6), and provoke mild local macrophage infiltration, suggesting an inherent risk of in vivo inflammation.

Niikura et al observed that AuNPs of varying diameters (15–50 nm) exhibited distinct recognition efficiency by antigen-presenting cells and differential T-cell activation when used as vaccine carriers, with ~40 nm AuNPs eliciting the strongest immune response, emphasizing particle size as a critical determinant of nanovaccine immunogenicity.[193] Moyano et al (2016) further reported that peptide- or protein-functionalized AuNPs significantly modulated cytokine expression and macrophage polarization under lipopolysaccharide (LPS) stimulation in vitro and in murine models, thereby reshaping immune-response patterns.[194]

Surface engineering has proven similarly impactful. Qie et al demonstrated that PEG coatings selectively reduce nanoparticle phagocytosis by distinct macrophage phenotypes (M1/M2), prolonging circulation and attenuating immune activation.[195] Lastly, La-Beck et al systematically analyzed the effects of nanoparticle size, charge, and shape on complement activation, identifying complement activation-related pseudoallergy as a notable clinical risk requiring careful evaluation in translational settings.[196]

Metabolism and Clearance Pathways of Nanomedicine Systems

The metabolic fate and clearance of nanocarriers are highly dependent on particle size and surface characteristics, primarily proceeding via renal filtration or hepatobiliary routes. Zhang et al demonstrated that glutathione (GSH)-stabilized Au nanoclusters with hydrodynamic diameters below ~5–6 nm undergo efficient glomerular filtration and urinary excretion, with negligible long-term retention in the RES, representing a rapid renal-clearance profile.[197]

In contrast, PEGylated AuNPs experience reduced renal filtration due to protein corona formation, exhibit extended circulation, and gradually accumulate in the liver and spleen. Animal studies have detected PEG-AuNPs in these organs even at day 28, accompanied by mild hepatic vacuolization and splenic apoptosis, highlighting risks of long-term retention and tissue responses.[198]

Li et al further revealed that surface chemistry dictates intrahepatic clearance pathways: PEG-coated AuNPs can traverse fenestrated liver sinusoids into the space of Disse for hepatocyte-mediated biliary excretion, whereas charged or rough-surfaced nanoparticles are preferentially sequestered by Kupffer cells, resulting in slower clearance and altered hepatic metabolic responses.[199]

These findings suggest that ultrasmall clusters favor rapid renal excretion, whereas surface-modified particles, while offering prolonged circulation, heighten the risk of hepatic and splenic retention and chronic toxicity. Notably, some ultrasmall nanoclusters can reside in muscle tissue as a temporary reservoir for weeks to months, followed by delayed systemic redistribution to organs such as the liver, spleen, heart, and lungs, potentially precipitating late-onset toxicity.[200]

Accordingly, nanomedicine design should balance pharmacokinetic optimization with long-term safety: For rapid clearance, particles < 6 nm with stable surface modifications are preferred. For prolonged circulation and targeted delivery, ~20 nm PEGylated nanoparticles are suitable but require chronic accumulation and toxicity assessment. Systems prone to storage and redistribution necessitate ≥90–120 days of pharmacokinetic and histopathological evaluation to assess latent risks.

Clinical Translation Challenges and Future Perspectives

Despite their remarkable promise in neurodegenerative diseases, oncology, and immunotherapy, nanomedicines face formidable hurdles on the path to clinical translation. Long-term safety remains the primary limiting factor. Preclinical studies indicate that certain nanocarriers can provoke immunogenicity or complement activation and exhibit persistent hepatic and splenic retention, phenomena that may be more complex and heterogeneous in humans.

Manufacturing and quality control also pose challenges. Particle size, surface chemistry, and protein corona formation critically influence in vivo distribution and clearance, yet scalable GMP-compliant production and standardized quality-control systems remain underdeveloped. Moreover, the scarcity of long-term pharmacokinetic and chronic toxicological data in both preclinical and clinical studies hampers comprehensive risk evaluation.

Recent advances in functionalized nanoplatforms have offered promising translational directions. For instance, nanotechnology-based traditional Chinese medicine immunotherapies have demonstrated robust immune activation and antitumor efficacy in gastrointestinal tumor models, highlighting the potential of nanotechnology to expand the clinical utility of conventional agents.[201] Similarly, PEG-coated magnetic nanoparticles loaded with curcumin exhibited excellent biocompatibility and anti-inflammatory effects in neuronal and macrophage models, suggesting that rational surface engineering and drug-loading strategies can enhance therapeutic efficacy while mitigating immunological risks, providing a blueprint for translational research in chronic inflammatory and neurodegenerative disorders.[202]

Looking ahead, successful clinical translation of nanomedicines will require breakthroughs in material degradability design, in vivo behavior tracking, and comprehensive long-term safety evaluation, coupled with multicenter clinical trials with extended follow-up to validate efficacy and safety. Achieving equilibrium between pharmacokinetic optimization and risk management is essential for nanomedicines to bridge the gap from bench to bedside.

Conclusion

Neurodegenerative diseases, characterized by complex etiologies, protracted courses, and limited therapeutic options, remain a major challenge in neuroscience and clinical medicine. The rapid advancement of nanotechnology has opened new avenues for intervention. A broad array of nanocarriers—including polymeric nanoparticles, liposomes, inorganic nanomaterials, and biomimetic systems—has shown promising drug-delivery and neuroprotective potential in models of Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. Through smart-responsive design, subcellular targeting, BBB penetration, and theranostic integration, nanomedicine systems enable precise drug delivery and multi-target intervention, offering unique advantages for early diagnosis and therapy.

Nevertheless, the journey from laboratory to clinic is fraught with challenges. Long-term safety, immunological risks, complex pharmacokinetics, and potential chronic toxicity remain central obstacles. Additionally, reproducible manufacturing, large-scale production, quality standardization, and long-term clinical monitoring are imperative for successful translation.

Future research must prioritize material degradability, the balance between delivery efficiency and safety, in vivo tracking of nanoparticle behavior, and rigorous long-term pharmacokinetic and toxicological assessments. Multicenter clinical trials with extended follow-up will be indispensable for validating both therapeutic efficacy and safety.

In summary, with continuous advances in materials science, pharmacokinetics, and neurobiology, nanotechnology is poised to become a pivotal tool for precision intervention in neurodegenerative diseases, ultimately offering patients safer, more effective, and accessible therapeutic strategies.

Abbreviations

BBB, blood–brain barrier; NDs, Neurodegenerative diseases; CNS, central nervous system; AD, Alzheimer's disease; PD, Parkinson's disease; HD, Huntington's disease; ALS, amyotrophic lateral sclerosis; NDDSs, Nanoparticle-based drug delivery systems; AMT, adsorptive-mediated transcytosis;TREM2, Triggering Receptor Expressed on Myeloid cells 2; RVG, Rabies Virus Glycoprotein; RMT, receptor-mediated transcytosis; ROS, reactive oxygen species; siRNA, small interfering RNA; SOD1, superoxide dismutase 1; ASO, antisense oligonucleotides.

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References

1. Dugger BN, Dickson DW. Pathology of neurodegenerative diseases. *Cold Spring Harbor Perspect Biol*. 2017;9(7):a028035. doi:10.1101/cshperspect.a028035
2. Agnello L, Ciaccio M. Neurodegenerative diseases: from molecular basis to therapy. *Int J Mol Sci*. 2022;23(21):12854. doi:10.3390/ijms232112854
3. Logroscino G, Urso D, Savica R. Descriptive epidemiology of neurodegenerative diseases: what are the critical questions? *Neuroepidemiology*. 2022;56(5):309–318. doi:10.1159/000525639
4. Cummings J, Aisen PS, DuBois B, et al. Drug development in Alzheimer's disease: the path to 2025. *Alzheimer's Res Ther*. 2016;8:39. doi:10.1186/s13195-016-0207-9
5. Marucci G, Buccioni M, Ben DD, Lambertucci C, Volpini R, Amenta F. Efficacy of acetylcholinesterase inhibitors in Alzheimer's disease. *Neuropharmacology*. 2021;190:108352. doi:10.1016/j.neuropharm.2020.108352
6. Murakami H, Shiraishi T, Umehara T, Omoto S, Iguchi Y. Recent advances in drug therapy for Parkinson's disease. *Intern Med*. 2023;62(1):33–42. doi:10.2169/internalmedicine.8940-21
7. LeWitt PA. Levodopa therapy for Parkinson's disease: pharmacokinetics and pharmacodynamics. *Movement Disorders*. 2015;30(1):64–72. doi:10.1002/mds.26082
8. Tzeplaeff L, Wilfling S, Requardt MV, Herdick M. Current State and Future Directions in the Therapy of ALS. *Cells*. 2023;12(11):1523. doi:10.3390/cells12111523
9. Sweeney MD, Sagare AP, Zlokovic BV. Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. *Nat Rev Neurol*. 2018;14(3):133–150. doi:10.1038/nrneurol.2017.188
10. Patabendige A, Janigro D. The role of the blood-brain barrier during neurological disease and infection. *Biochem Soc Trans*. 2023;51(2):613–626. doi:10.1042/BST20220830
11. Pardridge WM. The blood-brain barrier: bottleneck in brain drug development. *NeuroRx*. 2005;2(1):3–14. doi:10.1602/neurorx.2.1.3
12. Formicola B, Cox A, Magro RD, Masserini M, Re F. Nanomedicine for the treatment of Alzheimer's disease. *J Biomed Nanotechnol*. 2019;15(10):1997–2024. doi:10.1166/jbn.2019.2837
13. Ashok A, Andrabi SS, Mansoor S, Kuang Y, Kwon BK, Labhasetwar V. Antioxidant therapy in oxidative stress-induced neurodegenerative diseases: role of nanoparticle-based drug delivery systems in clinical translation. *Antioxidants*. 2022;11(2). doi:10.3390/antiox11020408
14. Saraiva C, Praça C, Ferreira R, Santos T, Ferreira L, Bernardino L. Nanoparticle-mediated brain drug delivery: overcoming blood-brain barrier to treat neurodegenerative diseases. *J Controlled Release*. 2016;235:34–47. doi:10.1016/j.jconrel.2016.05.044
15. Handa M, Singh A, Flora SJS, Shukla R. Stimuli-responsive polymeric nanosystems for therapeutic applications. *Curr Pharm Des*. 2022;28(11):910–921. doi:10.2174/1381612827666211208150210
16. Padmanabhan P, Palanivel M, Kumar A, et al. Nanotheranostic agents for neurodegenerative diseases. *Emerg Topics Life Sci*. 2020;4(6):645–675. doi:10.1042/ETLS20190141
17. Salvador J-P, Vilaplana L, Marco M-P. Nanobody: outstanding features for diagnostic and therapeutic applications. *Anal Bioanal Chem*. 2019;411(9):1703–1713. doi:10.1007/s00216-019-01633-4
18. Jin L, Nie L, Deng Y, Khana GJ, He N. The application of polymeric nanoparticles as drug delivery carriers to cells in neurodegenerative diseases. *Cell Proliferation*. 2025;58:e13804. doi:10.1111/cpr.13804

19. Pinto M, Silva V, Barreiro S, et al. Brain drug delivery and neurodegenerative diseases: polymeric PLGA-based nanoparticles as a forefront platform. *Ageing Res Rev*. 2022;79:101658. doi:10.1016/j.arr.2022.101658
20. Moazzam M, Zhang M, Hussain A, Yu X, Huang J, Huang Y. The landscape of nanoparticle-based siRNA delivery and therapeutic development. *Mol Ther*. 2024;32(2):284–312. doi:10.1016/j.ymthe.2024.01.005
21. Huang N, Lu S, Liu X-G, Zhu J, Wang Y-J, Liu R-T. PLGA nanoparticles modified with a BBB-penetrating peptide co-delivering Aβ generation inhibitor and curcumin attenuate memory deficits and neuropathology in Alzheimer's disease mice. *Oncotarget*. 2017;8(46):81001–81013. doi:10.18632/oncotarget.20944
22. Shin HJ, Kim IS, Choi SG, et al. Rejuvenating aged microglia by p16ink4a-siRNA-loaded nanoparticles increases amyloid-β clearance in animal models of Alzheimer's disease. *Mol Neurodegen*. 2024;19(1):25. doi:10.1186/s13024-024-00715-x
23. Campisi A, Sposito G, Pellitteri R, et al. Effect of unloaded and curcumin-loaded solid lipid nanoparticles on tissue transglutaminase isoforms expression levels in an experimental model of Alzheimer's disease. *Antioxidants*. 2022;11(10):1863. doi:10.3390/antiox11101863
24. Feng Q, Zhang X, Zhao X, et al. Intranasal delivery of pure nanodrug loaded liposomes for Alzheimer's disease treatment by efficiently regulating microglial polarization. *Small*. 2024;20(50):e2405781. doi:10.1002/smll.202405781
25. Sela M, Poley M, Mora-Raimundo P, et al. Brain-targeted liposomes loaded with monoclonal antibodies reduce alpha-synuclein aggregation and improve behavioral symptoms in Parkinson's disease. *Adv Mater*. 2023;35(51):e2304654. doi:10.1002/adma.202304654
26. Ulanova M, Gloag L, Bongers A, et al. Evaluation of dimercaptosuccinic acid-coated iron nanoparticles immunotargeted to amyloid beta as MRI contrast agents for the diagnosis of Alzheimer's disease. *Cells*. 2023;12(18):2279. doi:10.3390/cells12182279
27. Chen X, Guo X, Hao S, Yang T, Wang J. Iron oxide nanoparticles-loaded hyaluronic acid nanogels for MRI-aided Alzheimer's disease theranostics. *Arabian J. Chem*. 2022;15(6):103748. doi:10.1016/j.arabjc.2022.103748
28. Perich MP, Palma-Florez S, Solé C, et al. Polyoxometalate-decorated gold nanoparticles inhibit β-amyloid aggregation and cross the blood-brain barrier in a μphysiological model. *Nanomaterials*. 2023;13(19).
29. Ribeiro TDC, Sábio RM, Luiz MT, et al. Curcumin-loaded mesoporous silica nanoparticles dispersed in thermo-responsive hydrogel as potential alzheimer disease therapy. *Pharmaceutics*. 2022;14(9):1976. doi:10.3390/pharmaceutics14091976
30. Jiang S, Cai G, Yang Z, et al. Biomimetic nanovesicles as a dual gene delivery system for the synergistic gene therapy of Alzheimer's disease. *ACS nano*. 2024;18(18):11753–11768. doi:10.1021/acsnano.3c13150
31. Tang Y, Song X, Xiao M, et al. Inhibition of Aβ aggregation and tau phosphorylation with functionalized biomimetic nanoparticles for synergic Alzheimer's disease therapy. *ACS Appl Mater Interfaces*. 2024;16(45):61774–61786. doi:10.1021/acsami.4c16337
32. Huang J, Fu Y, Wang A, et al. Brain delivery of protein therapeutics by cell matrix-inspired biomimetic nanocarrier. *Adv Mater*. 2024;36(31): e2405323. doi:10.1002/adma.202405323
33. Hoyos-Ceballos GP, Ruozi B, Ottonelli I, et al. PLGA-PEG-ANG-2 nanoparticles for blood-brain barrier crossing: proof-of-concept study. *Pharmaceutics*. 2020;12(1):72. doi:10.3390/pharmaceutics12010072
34. Zhi K, Raji B, Nookala AR, et al. PLGA nanoparticle-based formulations to cross the blood-brain barrier for drug delivery: from R&D to cGMP. *Pharmaceutics*. 2021;13(4):500. doi:10.3390/pharmaceutics13040500
35. Su I-J, Chang H-Y, Wang H-C, Tsai K-J. A curcumin analog exhibits multiple biologic effects on the pathogenesis of Alzheimer's disease and improves behavior, inflammation, and β-amyloid accumulation in a mouse model. *Int J Mol Sci*. 2020;21(15):5459. doi:10.3390/ijms21155459
36. Xiong Z, Hongmei Z, Lu S, Yu L. Curcumin mediates presenilin-1 activity to reduce β-amyloid production in a model of Alzheimer's disease. *Pharmacol Rep*. 2011;63(5):1101–1108. doi:10.1016/S1734-1140(11)70629-6
37. Manap ASA, Tan ACW, Leong WH, et al. Synergistic effects of curcumin and piperine as potent acetylcholine and amyloidogenic inhibitors with significant neuroprotective activity in SH-SY5Y cells via computational molecular modeling and in vitro assay. *Front Aging Neurosci*. 2019;11:206. doi:10.3389/fnagi.2019.00206
38. Gu J, Yan C, Yin S, et al. Erythrocyte membrane-coated nanocarriers modified by TGN for Alzheimer's disease. *J Controlled Release*. 2024;366:448–459. doi:10.1016/j.jconrel.2023.12.030
39. Yan C, Gu J, Yin S, et al. Design and preparation of naringenin loaded functional biomimetic nano-drug delivery system for Alzheimer's disease. *J Drug Targeting*. 2024;32(1):80–92. doi:10.1080/1061186X.2023.2290453
40. Sweeney MD, Zhao Z, Montagne A, Nelson AR, Zlokovic BV. Blood-brain barrier: from physiology to disease and back. *Physiol Rev*. 2019;99 (1):21–78. doi:10.1152/physrev.00050.2017
41. Jain KK. Nanobiotechnology-based strategies for crossing the blood-brain barrier. *Nanomedicine*. 2012;7(8):1225–1233. doi:10.2217/ nnm.12.86
42. Dong X. Current strategies for brain drug delivery. *Theranostics*. 2018;8(6):1481–1493. doi:10.7150/thno.21254
43. Pardridge WM. Treatment of Parkinson's disease with biologics that penetrate the blood-brain barrier via receptor-mediated transport. *Front Aging Neurosci*. 2023;15:1276376. doi:10.3389/fnagi.2023.1276376
44. Choi ES, Shusta EV. Strategies to identify, engineer, and validate antibodies targeting blood-brain barrier receptor-mediated transcytosis systems for CNS drug delivery. *Expert Opin Drug Delivery*. 2023;20(12):1789–1800. doi:10.1080/17425247.2023.2286371
45. Blades R, Ittner LM, Tietz O. Peptides for trans-blood-brain barrier delivery. *J Labelled Compounds Radiopharm*. 2023;66(9):237–248. doi:10.1002/jlcr.4023
46. Srimanee A, Regberg J, Langel Ü. Application of CPPs for brain delivery. *Methods Mol Biol*. 2015;1324:349–356.
47. Pirhaghi M, Mamashli F, Moosavi-Movahedi F, et al. Cell-penetrating peptides: promising therapeutics and drug-delivery systems for neurodegenerative diseases. *Mol Pharmaceut*. 2024;21(5):2097–2117. doi:10.1021/acs.molpharmaceut.3c01167
48. Guo Q, Xu S, Yang P, et al. A dual-ligand fusion peptide improves the brain-neuron targeting of nanocarriers in Alzheimer's disease mice. *J Controlled Release*. 2020;320:347–362. doi:10.1016/j.jconrel.2020.01.039
49. Li J, Wei Y, Zhang C, et al. Cell-membrane-coated nanoparticles for targeted drug delivery to the brain for the treatment of neurological diseases. *Pharmaceutics*. 2023;15(2).
50. Soto C, Pritzkow S. Protein misfolding, aggregation, and conformational strains in neurodegenerative diseases. *Nat Neurosci*. 2018;21 (10):1332–1340. doi:10.1038/s41593-018-0235-9
51. Islam MT. Oxidative stress and mitochondrial dysfunction-linked neurodegenerative disorders. *Neurol Res*. 2017;39(1):73–82. doi:10.1080/ 01616412.2016.1251711

52. Stephenson J, Nutma E, Pvd V, Amor S. Inflammation in CNS neurodegenerative diseases. *Immunology*. 2018;154(2):204–219. doi:10.1111/imm.12922
53. Leng F, Edison P. Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? *Nat Rev Neurol*. 2021;17(3):157–172. doi:10.1038/s41582-020-00435-y
54. Kordower JH, Isacson O, Emerich DF. Cellular delivery of trophic factors for the treatment of Huntington's disease: is neuroprotection possible? *Exp Neurol*. 1999;159(1):4–20. doi:10.1006/exnr.1999.7156
55. Speidell A, Abid NB, Yano H. Brain-derived neurotrophic factor dysregulation as an essential pathological feature in Huntington's disease: mechanisms and potential therapeutics. *Biomedicines*. 2023;11(8):2275. doi:10.3390/biomedicines11082275
56. Stacchiotti C, Regnella SMD, Cinotti M, Spalloni A, Volpe E. Neuroinflammation and amyotrophic lateral sclerosis: recent advances in anti-inflammatory cytokines as therapeutic strategies. *Int J Mol Sci*. 2025;26(8):3854. doi:10.3390/ijms26083854
57. Long JM, Holtzman DM. Alzheimer Disease: an Update on Pathobiology and Treatment Strategies. *Cell*. 2019;179(2):312–339. doi:10.1016/j.cell.2019.09.001
58. Scheltens P, Strooper BD, Kivipelto M, et al. Alzheimer's disease. *Lancet*. 2021;397(10284):1577–1590. doi:10.1016/S0140-6736(20)32205-4
59. Cui G-H, Guo H-D, Li H, et al. RVG-modified exosomes derived from mesenchymal stem cells rescue memory deficits by regulating inflammatory responses in a mouse model of Alzheimer's disease. *Immun Ageing*. 2019;16:10. doi:10.1186/s12979-019-0150-2
60. Gao Y, Wang Z-Y, Zhang J, et al. RVG-peptide-linked trimethylated chitosan for delivery of siRNA to the brain. *Biomacromolecules*. 2014;15(3):1010–1018. doi:10.1021/bm401906p
61. Re F, Cambianica I, Zona C, et al. Functionalization of liposomes with ApoE-derived peptides at different density affects cellular uptake and drug transport across a blood-brain barrier model. *Nanomedicine*. 2011;7(5):551–559. doi:10.1016/j.nano.2011.05.004
62. Mathew A, Fukuda T, Nagaoka Y, et al. Curcumin loaded-PLGA nanoparticles conjugated with Tet-1 peptide for potential use in Alzheimer's disease. *PLoS One*. 2012;7(3):e32616. doi:10.1371/journal.pone.0032616
63. Saleh SR, Khamiss SE, Madhy SA, et al. Biochemical investigation and in silico analysis of the therapeutic efficacy of Ipriflavone through Tet-1 Surface-Modified-PLGA nanoparticles in streptozotocin-induced Alzheimer's like disease: reduced oxidative damage and etiological descriptors. *Int J Pharm*. 2025;669:125021. doi:10.1016/j.ijpharm.2024.125021
64. Saleh SR, Abd-Elmegied A, Madhy SA, et al. Brain-targeted Tet-1 peptide-PLGA nanoparticles for berberine delivery against STZ-induced Alzheimer's disease in a rat model: alleviation of hippocampal synaptic dysfunction, tau pathology, and amyloidogenesis. *Int J Pharm*. 2024;658:124218.
65. Silva RO, Counil H, Rabanel J-M, et al. Donepezil-loaded nanocarriers for the treatment of Alzheimer's Disease: superior efficacy of extracellular vesicles over polymeric nanoparticles. *Int J Nanomed*. 2024;19:1077–1096.
66. Parviz G, Guler E, Hazar-Yavuz AN, et al. Characterization and anti-Alzheimer's effect of donepezil-loaded chitosan/polyethylene glycol nanospheres. *J Drug Delivery Sci Technol*. 2025;108:106887. doi:10.1016/j.jddst.2025.106887
67. Handa M, Sanap SN, Bhatta RS, et al. Simultaneous intranasal codelivery of donepezil and memantine in a nanocolloidal carrier: optimization, pharmacokinetics, and pharmacodynamics studies. *Mol Pharmaceut*. 2023;20(9):4714–4728. doi:10.1021/acs.molpharmaceut.3c00454
68. Kaur A, Nigam K, Bhatnagar I, et al. Treatment of Alzheimer's diseases using donepezil nanoemulsion: an intranasal approach. *Drug Delivery Transl Res*. 2020;10(6):1862–1875.
69. Loureiro JA, Andrade S, Duarte A, et al. Resveratrol and grape extract-loaded solid lipid nanoparticles for the treatment of Alzheimer's disease. *Molecules*. 2017;22(2):277. doi:10.3390/molecules22020277
70. Abbas H, Refai H, Sayed NE, Rashed LA, Mousa MR, Zewail M. Superparamagnetic iron oxide loaded chitosan coated bilosomes for magnetic nose to brain targeting of resveratrol. *Int J Pharm*. 2021;610:121244.
71. Jia J, Zhao S, Zhao J, Gao Y. Engineered nanoparticles for the treatment of Alzheimer's disease. *Front Pharmacol*. 2025;16:1510798.
72. Wen X, Wang L, Liu Z, Liu Y, Hu J. Intracranial injection of PEG-PEI/ROCK II-siRNA improves cognitive impairment in a mouse model of Alzheimer's disease. *Int J Neurosci*. 2014;124(9):697–703. doi:10.3109/00207454.2013.877014
73. Wang P, Zheng X, Guo Q, et al. Systemic delivery of BACE1 siRNA through neuron-targeted nanocomplexes for treatment of Alzheimer's disease. *J Controlled Release*. 2018;279:220–233. doi:10.1016/j.jconrel.2018.04.034
74. Sun D, Li N, Zhang W, et al. Design of PLGA-functionalized quercetin nanoparticles for potential use in Alzheimer's disease. *Colloids Surf B*. 2016;148:116–129. doi:10.1016/j.colsurfb.2016.08.052
75. Liu G-Z, Niu -T-T, Yu Q, et al. Ginkgolide attenuates memory impairment and neuroinflammation by suppressing the NLRP3/caspase-1 pathway in Alzheimer's disease. *Aging*. 2023;15(19):10237–10252. doi:10.18632/aging.205072
76. Spilman P, Podlutskaya N, Hart MJ, et al. Inhibition of mTOR by rapamycin abolishes cognitive deficits and reduces amyloid-beta levels in a mouse model of Alzheimer's disease. *PLoS One*. 2010;5(4):e9979. doi:10.1371/journal.pone.0009979
77. Wang S, S-l Z, F-y M, et al. mTOR-mediated hyperphosphorylation of tau in the hippocampus is involved in cognitive deficits in streptozotocin-induced diabetic mice. *Metab Brain Dis*. 2014;29(3):729–736. doi:10.1007/s11011-014-9528-1
78. Lai C, Chen Z, Ding Y, et al. Rapamycin attenuated zinc-induced tau phosphorylation and oxidative stress in rats: involvement of dual mTOR/p70S6K and Nrf2/HO-1 pathways. *Front Immunol*. 2022;13:782434. doi:10.3389/fimmu.2022.782434
79. Chaparro CIP, Simões BT, Borges JP, Castanho MARB, Soares PIP, Neves V. A promising approach: magnetic nanosystems for Alzheimer's disease theranostics. *Pharmaceutics*. 2023;15(9):2316. doi:10.3390/pharmaceutics15092316
80. Kuang Y, Zhang J, Xiong M, et al. A novel nanosystem realizing curcumin delivery based on Fe3O4@Carbon dots nanocomposite for Alzheimer's disease therapy. *Front Bioeng Biotechnol*. 2020;8:614906. doi:10.3389/fbioe.2020.614906
81. Zhou ZD, Yi LX, Wang DQ, Lim TM, Tan EK. Role of dopamine in the pathophysiology of Parkinson's disease. *Transl Neurodegen*. 2023;12(1):44. doi:10.1186/s40035-023-00378-6
82. Mehra S, Sahay S, Maji SK. α-Synuclein misfolding and aggregation: implications in Parkinson's disease pathogenesis. *Biochim Biophys Acta Proteins Proteomics*. 2019;1867(10):890–908. doi:10.1016/j.bbapap.2019.03.001
83. Rocha EM, Miranda BD, Sanders LH. Alpha-synuclein: pathology, mitochondrial dysfunction and neuroinflammation in Parkinson's disease. *Neurobiol Dis*. 2018;109(Pt B):249–257. doi:10.1016/j.nbd.2017.04.004
84. Tambasco N, Romoli M, Calabresi P. Levodopa in Parkinson's disease: current status and future developments. *Curr Neuropharmacol*. 2018;16(8):1239–1252. doi:10.2174/1570159X15666170510143821

85. Monge-Fuentes V, Mayer AB, Lima MR, et al. Dopamine-loaded nanoparticle systems circumvent the blood-brain barrier restoring motor function in mouse model for Parkinson's disease. *Sci Rep*. 2021;11(1):15185. doi:10.1038/s41598-021-94175-8
86. Blandini F, Armentero M-T. Dopamine receptor agonists for Parkinson's disease. *Expert Opin Invest Drugs*. 2014;23(3):387–410. doi:10.1517/13543784.2014.869209
87. Battaglia L, Panciani PP, Muntoni E, et al. Lipid nanoparticles for intranasal administration: application to nose-to-brain delivery. *Expert Opin Drug Delivery*. 2018;15(4):369–378. doi:10.1080/17425247.2018.1429401
88. Tang S, Wang A, Yan X, et al. Brain-targeted intranasal delivery of dopamine with borneol and lactoferrin co-modified nanoparticles for treating Parkinson's disease. *Drug Delivery*. 2019;26(1):700–707. doi:10.1080/10717544.2019.1636420
89. Schlichtmann BW, Palanisamy BN, Malovic E, et al. Aggregation-inhibiting scFv-based therapies protect mice against AAV1/2-induced A53T-α-Synuclein overexpression. *Biomolecules*. 2023;13(8):1203. doi:10.3390/biom13081203
90. Palasz E, Wysocka A, Gasiorowska A, Chalimoniuk M, Niewiadomski W, Niewiadomska G. BDNF as a promising therapeutic agent in Parkinson's disease. *Int J Mol Sci*. 2020;21(3):1170. doi:10.3390/ijms21031170
91. Allen SJ, Watson JJ, Shoemark DK, Barua NU, GDNF PNK. NGF and BDNF as therapeutic options for neurodegeneration. *Pharmacol Ther*. 2013;138(2):155–175. doi:10.1016/j.pharmthera.2013.01.004
92. Tuominen RK, Renko J-M. Biomarkers of Parkinson's disease in perspective of early diagnosis and translation of neurotrophic therapies. *Basic Clin Physiol Pharmacol*. 2024;135(3):271–284. doi:10.1111/bcpt.14042
93. Rotondo R, Proietti S, Perluigi M, et al. Physical activity and neurotrophic factors as potential drivers of neuroplasticity in Parkinson's Disease: a systematic review and meta-analysis. *Ageing Res Rev*. 2023;92:102089.
94. Zhang Y, Pardridge WM. Near complete rescue of experimental Parkinson's disease with intravenous, non-viral GDNF gene therapy. *Pharm Res*. 2009;26(5):1059–1063. doi:10.1007/s11095-008-9815-9
95. Yue P, Miao W, Gao L, Zhao X, Teng J. Ultrasound-Triggered Effects of the Microbubbles Coupled to GDNF Plasmid-Loaded PEGylated Liposomes in a Rat Model of Parkinson's Disease. *Front Neurosci*. 2018;12:222. doi:10.3389/fnins.2018.00222
96. Zhai L, Gao Y, Yang H, et al. A ROS-Responsive nanoparticle for nuclear gene delivery and autophagy restoration in Parkinson's disease therapy. *Biomaterials*. 2025;321:123345. doi:10.1016/j.biomaterials.2025.123345
97. McColgan P, Tabrizi SJ. Huntington's disease: a clinical review. *Eur J Neurol*. 2018;25(1):24–34. doi:10.1111/ene.13413
98. Jimenez-Sanchez M, Licitra F, Underwood BR, Rubinsztein DC. Huntington's disease: mechanisms of pathogenesis and therapeutic strategies. *Cold Spring Harbor Perspect Med*. 2017;7(7).
99. Evers MM, Toonen LJA. Roon-Mom WMCv. Antisense oligonucleotides in therapy for neurodegenerative disorders. *Adv Drug Delivery Rev*. 2015;87:90–103.
100. Tabrizi SJ, Leavitt BR, Landwehrmeyer GB, et al. Targeting Huntingtin Expression in Patients with Huntington's Disease. *New Engl J Med*. 2019;380(24):2307–2316. doi:10.1056/NEJMoa1900907
101. Morelli KH, Wu Q, Gosztyla ML, et al. An RNA-targeting CRISPR-Cas13d system alleviates disease-related phenotypes in Huntington's disease models. *Nat Neurosci*. 2023;26(1):27–38. doi:10.1038/s41593-022-01207-1
102. Joshi AS, Singh V, Gahane A, Thakur AK. Biodegradable nanoparticles containing mechanism based peptide inhibitors reduce polyglutamine aggregation in cell models and alleviate motor symptoms in a Drosophila model of Huntington's disease. *ACS Chem Neurosci*. 2019;10(3):1603–1614. doi:10.1021/acschemneuro.8b00545
103. Godinho BMDC, Ogier JR, Darcy R, O'Driscoll CM, Cryan JF. Self-assembling modified β-cyclodextrin nanoparticles as neuronal siRNA delivery vectors: focus on Huntington's disease. *Mol Pharmaceut*. 2013;10(2):640–649. doi:10.1021/mp3003946
104. Amin MA, Zehravi M, Sweilam SH, et al. Neuroprotective potential of epigallocatechin gallate in neurodegenerative diseases: insights into molecular mechanisms and clinical relevance. *Brain Res*. 2025;1860:149693. doi:10.1016/j.brainres.2025.149693
105. Rani A, Saini V, Patra P, et al. Epigallocatechin Gallate: a multifaceted molecule for neurological disorders and neurotropic viral infections. *ACS Chem Neurosci*. 2023;14(17):2968–2980. doi:10.1021/acschemneuro.3c00368
106. Jackrel ME, Shorter J. Shock and awe: unleashing the heat shock response to treat Huntington disease. *J Clin Invest*. 2011;121(8):2972–2975. doi:10.1172/JCI59190
107. Stavrides P, Goulbourne CN, Peddy J, et al. mTOR inhibition in Q175 Huntington's disease model mice facilitates neuronal autophagy and mutant huntingtin clearance. *bioRxiv*. 2025.
108. Ehrnhoefer DE, Duennwald M, Markovic P, et al. Green tea (-)-epigallocatechin-gallate modulates early events in huntingtin misfolding and reduces toxicity in Huntington's disease models. *Human Mol Genetics*. 2006;15(18):2743–2751. doi:10.1093/hmg/ddl210
109. Cano A, Ettcheto M, Espina M, et al. Epigallocatechin-3-gallate PEGylated poly(lactic-co-glycolic) acid nanoparticles mitigate striatal pathology and motor deficits in 3-nitropropionic acid intoxicated mice. *Nanomedicine*. 2021;16(1):19–35. doi:10.2217/nnm-2020-0239
110. Sava V, Fihurka O, Khvorova A, Sanchez-Ramos J. Enriched chitosan nanoparticles loaded with siRNA are effective in lowering Huntington's disease gene expression following intranasal administration. *Nanomedicine*. 2020;24:102119. doi:10.1016/j.nano.2019.102119
111. Mendonça MCP, Cronin MF, Cryan JF, O'Driscoll CM. Modified cyclodextrin-based nanoparticles mediated delivery of siRNA for huntingtin gene silencing across an in vitro BBB model. *Eur J Pharm Biopharm*. 2021;169:309–318. doi:10.1016/j.ejpb.2021.11.003
112. Feldman EL, Goutman SA, Petri S, et al. Amyotrophic lateral sclerosis. *Lancet*. 2022;400(10360):1363–1380. doi:10.1016/S0140-6736(22)01272-7
113. Stansberry WM, Pierchala BA. Neurotrophic factors in the physiology of motor neurons and their role in the pathobiology and therapeutic approach to amyotrophic lateral sclerosis. *Front Mol Neurosci*. 2023;16:1238453. doi:10.3389/fnmol.2023.1238453
114. Cao MC, Cawston EE, Chen G, et al. Serum biomarkers of neuroinflammation and blood-brain barrier leakage in amyotrophic lateral sclerosis. *BMC Neurol*. 2022;22(1):216. doi:10.1186/s12883-022-02730-1
115. Leyton-Jaimes MF, Ivert P, Hoeber J, et al. Empty mesoporous silica particles significantly delay disease progression and extend survival in a mouse model of ALS. *Sci Rep*. 2020;10(1):20675. doi:10.1038/s41598-020-77578-x
116. Mazibuko Z, Choonara YE, Kumar P, et al. A review of the potential role of nano-enabled drug delivery technologies in amyotrophic lateral sclerosis: lessons learned from other neurodegenerative disorders. *J Pharmaceut Sci*. 2015;104(4):1213–1229. doi:10.1002/jps.24322
117. Zhou J, Li A, Li X, Yi J. Dysregulated mitochondrial Ca2+ and ROS signaling in skeletal muscle of ALS mouse model. *Arch Biochem Biophys*. 2019;663:249–258. doi:10.1016/j.abb.2019.01.024

118. Aguiar B, Alfenim AR, Machado CS, et al. Exploring nano-delivery systems to enhance the edaravone performance in amyotrophic lateral sclerosis treatment. *Int J Mol Sci*. 2025;26(5):2146. doi:10.3390/ijms26052146
119. Medina DX, Chung EP, Teague CD, Bowser R, Sirianni RW. Intravenously administered, retinoid activating nanoparticles increase lifespan and reduce neurodegeneration in the SOD1G93A mouse model of ALS. *Front Bioeng Biotechnol*. 2020;8:224. doi:10.3389/fbioe.2020.00224
120. Berdyński M, Miszta P, Safranow K, et al. SOD1 mutations associated with amyotrophic lateral sclerosis analysis of variant severity. *Sci Rep*. 2022;12(1):103. doi:10.1038/s41598-021-03891-8
121. Hallegger M, Chakrabarti AM, Lee FCY, et al. TDP-43 condensation properties specify its RNA-binding and regulatory repertoire. *Cell*. 2021;184(18):4680–4696.e4622. doi:10.1016/j.cell.2021.07.018
122. Xiao X, Li M, Ye Z, He X, Wei J, Zha Y. FUS gene mutation in amyotrophic lateral sclerosis: a new case report and systematic review. *Amyotrophic Lateral Scler Frontttemp Degen*. 2024;25(1–2):1–15. doi:10.1080/21678421.2023.2272170
123. Möller K, Müller K, Engelke H, Bräuchle C, Wagner E, Bein T. Highly efficient siRNA delivery from core-shell mesoporous silica nanoparticles with multifunctional polymer caps. *Nanoscale*. 2016;8(7):4007–4019. doi:10.1039/C5NR06246B
124. Wu -C-C, Lee P-T, Kao T-J, et al. Upregulation of Znf179 acetylation by SAHA protects cells against oxidative stress. *Redox Biol*. 2018;19:74–80. doi:10.1016/j.redox.2018.08.001
125. Sukprasansap M, Chanvorachote P, Tencomnao T. Cleistocalyx nervosum var. paniala berry fruit protects neurotoxicity against endoplasmic reticulum stress-induced apoptosis. *Food Chem Toxicol*. 2017;103:279–288. doi:10.1016/j.fct.2017.03.025
126. Fiadeiro MB, Diogo JC, Silva AA, Kim Y-S, Cristóvão AC. NADPH oxidases in neurodegenerative disorders: mechanisms and therapeutic opportunities. *Antioxid Redox Signaling*. 2024;41(7–9):522–541. doi:10.1089/ars.2023.0002
127. Zipfel P, Rochais C, Baranger K, Rivera S, Dallemagne P. Matrix metalloproteinases as new targets in Alzheimer's disease: opportunities and challenges. *J Med Chem*. 2020;63(19):10705–10725. doi:10.1021/acs.jmedchem.0c00352
128. Pichla M, Bartosz G, Stefaniuk I. Sadowska-Bartosz I. pH-responsive redox nanoparticles protect SH-SY5Y cells at lowered pH in a cellular model of Parkinson's disease. *Molecules*. 2021;26(3):543. doi:10.3390/molecules26030543
129. Gao C, Jiang J, Tan Y, Chen S. Microglia in neurodegenerative diseases: mechanism and potential therapeutic targets. *Signal Transduct Targe Ther*. 2023;8(1):359. doi:10.1038/s41392-023-01588-0
130. Deirram N, Zhang C, Kermaniyan SS, Johnston APR, Such GK. pH-responsive polymer nanoparticles for drug delivery. *Macromol Rapid Commun*. 2019;40(10):e1800917. doi:10.1002/marc.201800917
131. Elhabak M, Salama AAA, Salama AH. Nose-to-brain delivery of galantamine loaded nanospray dried polyacrylic acid/taurodeoxycholate mixed matrix as a protective therapy in lipopolysaccharide-induced Alzheimer's in mice model. *Int J Pharm*. 2023;632:122588. doi:10.1016/j.ijpharm.2023.122588
132. Gisbert-Garzarán M, Berkmann JC, Giasafaki D, et al. Engineered pH-responsive mesoporous carbon nanoparticles for drug delivery. *ACS Appl Mater Interfaces*. 2020;12(13):14946–14957. doi:10.1021/acsami.0c01786
133. Singh A, Kukreti R, Saso L, Kukreti S. Oxidative stress: a key modulator in neurodegenerative diseases. *Molecules*. 2019;24(8):1583. doi:10.3390/molecules24081583
134. Zhou Y, Zhen Y, Wang G, Liu B. Deconvoluting the complexity of Reactive Oxygen Species (ROS) in neurodegenerative diseases. *Front Neuroanatomy*. 2022;16:910427. doi:10.3389/fnana.2022.910427
135. Ballance WC, Qin EC, Chung HJ, Gillette MU, Kong H. Reactive oxygen species-responsive drug delivery systems for the treatment of neurodegenerative diseases. *Biomaterials*. 2019;217:119292. doi:10.1016/j.biomaterials.2019.119292
136. Lei L, Tu Q, Zhang X, et al. Stimulus-responsive curcumin-based polydopamine nanoparticles for targeting Parkinson's disease by modulating α-synuclein aggregation and reactive oxygen species. *Chem Eng J*. 2023;461:141606. doi:10.1016/j.cej.2023.141606
137. Kim D, Yoo JM, Hwang H, et al. Graphene quantum dots prevent α-synucleinopathy in Parkinson's disease. *Nature Nanotechnol*. 2018;13(9):812–818. doi:10.1038/s41565-018-0179-y
138. Si X, Dai S, Fang Y, et al. Matrix metalloproteinase-9 inhibition prevents aquaporin-4 depolarization-mediated glymphatic dysfunction in Parkinson's disease. *J Adv Res*. 2024;56:125–136. doi:10.1016/j.jare.2023.03.004
139. Almeida MF, Bahr BA, Kinsey ST. Endosomal-lysosomal dysfunction in metabolic diseases and Alzheimer's disease. *Int Rev Neurobiol*. 2020;154:303–324.
140. Walczak-Nowicka ŁJ, Herbet M. Acetylcholinesterase inhibitors in the treatment of neurodegenerative diseases and the role of acetylcholinesterase in their pathogenesis. *Int J Mol Sci*. 2021;22(17).
141. Hu Q, Katti PS, Gu Z. Enzyme-responsive nanomaterials for controlled drug delivery. *Nanoscale*. 2014;6(21):12273–12286. doi:10.1039/C4NR04249B
142. Alvarez A, Opazo C, Alarcón R, Garrido J, Inestrosa NC. Acetylcholinesterase promotes the aggregation of amyloid-beta-peptide fragments by forming a complex with the growing fibrils. *J Mol Biol*. 1997;272(3):348–361. doi:10.1006/jmbi.1997.1245
143. Bartolini M, Bertucci C, Cavrini V, Andrisano V. beta-Amyloid aggregation induced by human acetylcholinesterase: inhibition studies. *Biochem Pharmacol*. 2003;65(3):407–416. doi:10.1016/S0006-2952(02)01514-9
144. Muñoz-Torrero D. Acetylcholinesterase inhibitors as disease-modifying therapies for Alzheimer's disease. *Curr Med Chem*. 2008;15(24):2433–2455. doi:10.2174/092986708785909067
145. Dinamarca MC, Sagal JP, Quintanilla RA, Godoy JA, Arrázola MS, Inestrosa NC. Amyloid-beta-Acetylcholinesterase complexes potentiate neurodegenerative changes induced by the Abeta peptide. Implications for the pathogenesis of Alzheimer's disease. *Mol Neurodegen*. 2010;5:4. doi:10.1186/1750-1326-5-4
146. García-Ayllón M-S, Small DH, Avila J, Sáez-Valero J. Revisiting the role of acetylcholinesterase in alzheimer's Disease: cross-talk with P-tau and β-amyloid. *Front Mol Neurosci*. 2011;4:22. doi:10.3389/fnmol.2011.00022
147. Hook V, Yoon M, Mosier C, et al. Cathepsin B in neurodegeneration of Alzheimer's disease, traumatic brain injury, and related brain disorders. *Biochim Biophys Acta Proteins Proteomics*. 2020;1868(8):140428. doi:10.1016/j.bbapap.2020.140428
148. Ni J, Lan F, Xu Y, Nakanishi H, Li X. Extralysosomal cathepsin B in central nervous system: mechanisms and therapeutic implications. *Brain Pathol*. 2022;32(5):e13071. doi:10.1111/bpa.13071
149. Bunk J, Huarcaya SP, Drobny A, et al. Cathepsin D variants associated with neurodegenerative diseases show dysregulated functionality and modified α-Synuclein degradation properties. *Front Cell Develop Biol*. 2021;9:581805. doi:10.3389/fcell.2021.581805

150. Domenico FD, Tramutola A, Perluigi M. Cathepsin D as a therapeutic target in Alzheimer's disease. *Expert Opin Therap Targets*. 2016;20 (12):1393–1395. doi:10.1080/14728222.2016.1252334
151. Mueller-Steiner S, Zhou Y, Arai H, et al. Antiamyloidogenic and neuroprotective functions of cathepsin B: implications for Alzheimer's disease. *Neuron*. 2006;51(6):703–714. doi:10.1016/j.neuron.2006.07.027
152. Sevlever D, Jiang P, Yen S-HC. Cathepsin D is the main lysosomal enzyme involved in the degradation of alpha-synuclein and generation of its carboxy-terminally truncated species. *Biochemistry*. 2008;47(36):9678–9687. doi:10.1021/bi800699v
153. Guo J, Liu X-Y, Yang -S-S, et al. Roles of C/EBPβ/AEP in neurodegenerative diseases. *Curr Topics Med Chem*. 2025;25. doi:10.2174/0115680266357822250119172351
154. Zhang Z, Tian Y, Ye K. δ-secretase in neurodegenerative diseases: mechanisms, regulators and therapeutic opportunities. *Transl Neurodegen*. 2020;9:1. doi:10.1186/s40035-019-0179-3
155. Liu P, Wang Z-H, Kang SS, et al. High-fat diet-induced diabetes couples to Alzheimer's disease through inflammation-activated C/EBPβ/AEP pathway. *Mol Psychiatry*. 2022;27(8):3396–3409. doi:10.1038/s41380-022-01600-z
156. Xiong J, Zhang Z, Ye K. C/EBPβ/AEP signaling drives Alzheimer's disease pathogenesis. *Neurosci Bull*. 2023;39(7):1173–1185. doi:10.1007/s12264-023-01025-w
157. Qian Z, Li B, Meng X, et al. Inhibition of asparagine endopeptidase (AEP) effectively treats sporadic Alzheimer's disease in mice. *Neuropsychopharmacology*. 2024;49(3):620–630. doi:10.1038/s41386-023-01774-2
158. Li L, Dawson VL, Dawson TM. Gastrointestinal tract cleavage of α-synuclein by asparaginyl endopeptidase leads to Parkinson's disease. *Neuron*. 2024;112(21):3516–3518. doi:10.1016/j.neuron.2024.10.015
159. Zhang Z, Xie M, Ye K. Asparagine endopeptidase is an innovative therapeutic target for neurodegenerative diseases. *Expert Opin Therap Targets*. 2016;20(10):1237–1245. doi:10.1080/14728222.2016.1182990
160. Meng X, Li B, Wang M, Zheng W, Ye K. Development of asparagine endopeptidase inhibitors for treating neurodegenerative diseases. *Trends Mol Med*. 2025;31(4):359–372. doi:10.1016/j.molmed.2025.01.009
161. Buck AC, Maarman GJ, Dube A, Bardien S. Mitochondria targeted nanoparticles for the treatment of mitochondrial dysfunction-associated brain disorders. *Front Bioeng Biotechnol*. 2025;13:1563701. doi:10.3389/fbioe.2025.1563701
162. González LF, Bevilacqua LE, Naves R. Nanotechnology-based drug delivery strategies to repair the mitochondrial function in neuroinflammatory and neurodegenerative diseases. *Pharmaceutics*. 2021;13(12). doi:10.3390/pharmaceutics13122055
163. Khan T, Waseem R, Zehra Z, et al. Mitochondrial dysfunction: pathophysiology and mitochondria-targeted drug delivery approaches. *Pharmaceutics*. 2022;14(12):2657. doi:10.3390/pharmaceutics14122657
164. Keethedeth N, Shenoi RA. Mitochondria-targeted nanotherapeutics: a new frontier in neurodegenerative disease treatment. *Mitochondrion*. 2025;81:102000. doi:10.1016/j.mito.2024.102000
165. Zhang S, Li M, Li Y, et al. Mitochondria-targeted nanovesicles for ursodeoxycholic acid delivery to combat neurodegeneration by ameliorating mitochondrial dysfunction. *J Nanobiotechnol*. 2025;23(1):202. doi:10.1186/s12951-025-03258-5
166. Nixon RA, Rubinsztein DC. Mechanisms of autophagy-lysosome dysfunction in neurodegenerative diseases. *Nat Rev Mol Cell Biol*. 2024;25 (11):926–946. doi:10.1038/s41580-024-00757-5
167. Singh NA, Bhardwaj V, Ravi C, Ramesh N, Mandal AKA, Khan ZA. EGCG nanoparticles attenuate aluminum chloride induced neurobehavioral deficits, beta amyloid and tau pathology in a rat model of Alzheimer's Disease. *Front Aging Neurosci*. 2018;10:244. doi:10.3389/fnagi.2018.00244
168. Ren C, Li D, Zhou Q, Hu X. Mitochondria-targeted TPP-MoS2 with dual enzyme activity provides efficient neuroprotection through M1/M2 microglial polarization in an Alzheimer's disease model. *Biomaterials*. 2020;232:119752. doi:10.1016/j.biomaterials.2019.119752
169. Cisneros J, Belton TB, Shum GC, Molakal CG, Wong YC. Mitochondria-lysosome contact site dynamics and misregulation in neurodegenerative diseases. *Trends Neurosci*. 2022;45(4):312–322. doi:10.1016/j.tins.2022.01.005
170. Cano A, Ettcheto M, Chang J-H, et al. Dual-drug loaded nanoparticles of Epigallocatechin-3-gallate (EGCG)/Ascorbic acid enhance therapeutic efficacy of EGCG in a APPswe/PS1dE9 Alzheimer's disease mice model. *J Controlled Release*. 2019;301:62–75. doi:10.1016/j.jconrel.2019.03.010
171. Lim CKW, Gapinske M, Brooks AK, et al. Treatment of a mouse model of ALS by in vivo base editing. *Mol Ther*. 2020;28(4):1177–1189. doi:10.1016/j.ymthe.2020.01.005
172. Gaj T, Ojala DS, Ekman FK, Byrne LC, Limsirichai P, Schaffer DV. In vivo genome editing improves motor function and extends survival in a mouse model of ALS. *Sci Adv*. 2017;3(12):eaar3952. doi:10.1126/sciadv.aar3952
173. Kim A, Lalonde K, Truesdell A, et al. New avenues for the treatment of Huntington's disease. *Int J Mol Sci*. 2021;22(16).
174. Oliveira C, Ribeiro AJ, Veiga F, Silveira I. Recent advances in nucleic acid-based delivery: from bench to clinical trials in genetic diseases. *J Biomed Nanotechnol*. 2016;12(5):841–862. doi:10.1166/jbn.2016.2245
175. Pandey SK, Singh RK. Recent developments in nucleic acid-based therapies for Parkinson's disease: current status, clinical potential, and future strategies. *Front Pharmacol*. 2022;13:986668. doi:10.3389/fphar.2022.986668
176. Jamwal S, Elsworth JD, Rahi V, Kumar P. Gene therapy and immunotherapy as promising strategies to combat Huntington's disease-associated neurodegeneration: emphasis on recent updates and future perspectives. *Expert Rev Neurotherap*. 2020;20(11):1123–1141. doi:10.1080/14737175.2020.1801424
177. Keeler AM, Zieger M, Semple C, et al. Intralingual and intrapleural AAV gene therapy prolongs survival in a SOD1 ALS mouse model. *Mol Ther Meth Clin Develop*. 2020;17:246–257. doi:10.1016/j.omtm.2019.12.007
178. Wang Q, Cheng S, Qin F, Fu A, Fu C. Application progress of RVG peptides to facilitate the delivery of therapeutic agents into the central nervous system. *RSC Adv*. 2021;11(15):8505–8515. doi:10.1039/D1RA00550B
179. Lin Y, Li C, Chen Y, et al. RNA-Targeting CRISPR/CasRx system relieves disease symptoms in Huntington's disease models. *Mol Neurodegen*. 2025;20(1):4. doi:10.1186/s13024-024-00794-w
180. Shojaei M, Schaefer R, Schlepckow K, et al. PET imaging of microglia in Alzheimer's disease using copper-64 labeled TREM2 antibodies. *Theranostics*. 2024;14(16):6319–6336. doi:10.7150/thno.97149
181. Naganuma F, Murata D, Inoue M, et al. A novel near-infrared fluorescence probe THK-565 enables in vivo detection of amyloid deposits in Alzheimer's disease mouse model. *Mol Imaging Biol*. 2023;25(6):1115–1124. doi:10.1007/s11307-023-01843-4

182. Tajahmadi S, Molavi H, Ahmadijokani F, et al. Metal-organic frameworks: a promising option for the diagnosis and treatment of Alzheimer's disease. *J Controlled Release*. 2023;353:1–29. doi:10.1016/j.jconrel.2022.11.002
183. Yuan X, Jia Z, Li J, et al. A diselenide bond-containing ROS-responsive ruthenium nanoplatform delivers nerve growth factor for Alzheimer's disease management by repairing and promoting neuron regeneration. *J Mat Chem B*. 2021;9(37):7835–7847. doi:10.1039/D1TB01290H
184. Yang X, Yang W, Xia X, et al. Intranasal delivery of BACE1 siRNA and Rapamycin by dual targets modified nanoparticles for Alzheimer's disease therapy. *Small*. 2022;18(30):e2203182. doi:10.1002/smll.202203182
185. Gao C, Xiong R, Zhang Z-Y, et al. Hybrid nanostructures for neurodegenerative disease theranostics: the art in the combination of biomembrane and non-biomembrane nanostructures. *Transl Neurodegen*. 2024;13(1):43. doi:10.1186/s40035-024-00436-7
186. Pan R, Chen D, Hou L, Hu R, Jiao Z. Small extracellular vesicles: a novel drug delivery system for neurodegenerative disorders. *Front Aging Neurosci*. 2023;15:1184435. doi:10.3389/fnagi.2023.1184435
187. Sonavane G, Tomoda K, Makino K. Biodistribution of colloidal gold nanoparticles after intravenous administration: effect of particle size. *Colloids Surf B*. 2008;66(2):274–280. doi:10.1016/j.colsurfb.2008.07.004
188. Jakic K, Selc M, Razga F, et al. Long-term accumulation, biological effects and toxicity of BSA-coated gold nanoparticles in the mouse liver, spleen, and kidneys. *Int J Nanomed*. 2024;19:4103–4120. doi:10.2147/IJN.S443168
189. Yang L, Kuang H, Zhang W, Aguilar ZP, Wei H, Xu H. Comparisons of the biodistribution and toxicological examinations after repeated intravenous administration of silver and gold nanoparticles in mice. *Sci Rep*. 2017;7(1):3303. doi:10.1038/s41598-017-03015-1
190. Takeuchi I, Onaka H, Makino K. Biodistribution of colloidal gold nanoparticles after intravenous injection: effects of PEGylation at the same particle size. *Bio-Med Mater Eng*. 2018;29(2):205–215. doi:10.3233/BME-171723
191. Daems N, Verlinden B, Hoecke KV, et al. In vivo pharmacokinetics, biodistribution and toxicity of antibody-conjugated gold nanoparticles in healthy mice. *J Biomed Nanotechnol*. 2020;16(6):985–996. doi:10.1166/jbn.2020.2928
192. Chen H, Dorrigan A, Saad S, Hare DJ, Cortie MB, Valenzuela SM. In vivo study of spherical gold nanoparticles: inflammatory effects and distribution in mice. *PLoS One*. 2013;8(2):e58208. doi:10.1371/journal.pone.0058208
193. Niikura K, Matsunaga T, Suzuki T, et al. Gold nanoparticles as a vaccine platform: influence of size and shape on immunological responses in vitro and in vivo. *ACS nano*. 2013;7(5):3926–3938. doi:10.1021/nn3057005
194. Moyano DF, Liu Y, Ayaz F, et al. Immunomodulatory effects of coated gold nanoparticles in LPS-stimulated in vitro and in vivo murine model systems. *Chem*. 2016;1(2):320–327. doi:10.1016/j.chempr.2016.07.007
195. Qie Y, Yuan H, CAv R, et al. Surface modification of nanoparticles enables selective evasion of phagocytic clearance by distinct macrophage phenotypes. *Sci Rep*. 2016;6:26269. doi:10.1038/srep26269
196. La-beck NM, Islam MR, Markiewski MM. Nanoparticle-induced complement activation: implications for cancer nanomedicine. *Front Immunol*. 2020;11:603039. doi:10.3389/fimmu.2020.603039
197. Zhang X-D, Wu D, Shen X, Liu P-X, Fan F-Y, Fan S-J. In vivo renal clearance, biodistribution, toxicity of gold nanoclusters. *Biomaterials*. 2012;33(18):4628–4638. doi:10.1016/j.biomaterials.2012.03.020
198. Kozics K, Sramkova M, Kopecka K, et al. Pharmacokinetics, biodistribution, and biosafety of PEGylated gold nanoparticles in vivo. *Nanomaterials*. 2021;11(7):1702. doi:10.3390/nano11071702
199. Li X, Wang B, Zhou S, et al. Surface chemistry governs the sub-organ transfer, clearance and toxicity of functional gold nanoparticles in the liver and kidney. *J Nanobiotechnol*. 2020;18(1):45. doi:10.1186/s12951-020-00599-1
200. Zhang X-D, Luo Z, Chen J, et al. Storage of gold nanoclusters in muscle leads to their biphasic in vivo clearance. *Small*. 2015;11(14):1683–1690. doi:10.1002/smll.201402233
201. Peng L, Liang Y, Zhang Q, Guo X, Gao Z, Cui D. Nanoparticle-based Traditional Chinese Medicine for immunotherapy in gastrointestinal tumors. *Nano Biomed Eng*. 2025;17(2):161–178. doi:10.26599/NBE.2025.9290115
202. Abdelmonem M, Saad N, Teh HF, et al. Curcumin-loaded PEG-coated magnetite nanoparticles synthesized from Theobroma cocoa: neuronal biocompatibility and anti-inflammatory properties in SH-SY5Y and RAW 264.7 cells. *Nano Biomed Eng*. 2024;16(3):386–401. doi:10.26599/NBE.2024.9290099