Nanotechnology approaches neurodegenerative diseases

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Long-lasting neuronal degeneration, which leads to severe motor and cognitive deficits, is a characteristic of neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), and Amyotrophic Lateral Sclerosis (ALS). They pose major social, demographic, and public health problems due to their increased prevalence with demographic transition. For many neurological diseases, the diagnosis and therapy of which remain challenging to date, nanotechnology has emerged as an innovative strategy in the past years. This review presents and discusses in detail different approaches in which nanotechnology is currently employed for neurodegenerative disease therapy, including site-specific drug delivery across the blood-brain barrier (BBB), and early diagnostics utilizing nano-scaled biosensors or imaging tools. Engineered nanocarriers, such as liposomes, dendrimers, gold nanoparticles, and solid lipid nanoparticles, have been encouragingly reported in the delivery of neuroprotective agents, gene editing agents, and drugs. Even recent research studies are starting to confirm these approaches with the potential to arrest or alter the course of the disease. The merging of diagnosis and therapy of nanotechnology (nanotheranostics) provides opportunities for personalized diagnosis and treatment with real-time monitoring, and the development of biocompatible materials helps to overcome safety challenges. Concerted progress in nanomedicine, artificial intelligence, and regulatory science is accelerating the translation of such breakthroughs to the clinic. Precision medicine approaches, interdisciplinary collaboration, and fusion with neurotechnology constitute the future of neuromedicine.

Keywords: Nanotechnology, Neurodegenerative Diseases, Blood-Brain Barrier, Targeted Drug Delivery, Nanotheranostics

ARTICLE HISTORY

Received: July 28, 2025
Revised: August 23, 2025
Accepted: August 23, 2025

CORRESPONDENCE TO

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DOI: 10.21608/nasj.2025.408057.1010

INTRODUCTION

The slow degeneration and malfunctioning of neurons define as neurodegenerative diseases (NDs), including Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). These diseases significantly affect world morbidity, disability, and death rates. According to the World Health Organization, more than 55 million individuals globally are affected by dementia, a number predicted to triple by 2050 because of anticipated population aging. Dementia affects around 5-8% of individuals over 60 years of age, with nearly 10 million new cases diagnosed annually, primarily from AD [1]. Over 10 million people are afflicted with PD, which has overtaken other neurological ailments in terms of growth rate regarding prevalence and disability-adjusted life years. ALS is a life-threatening neurodegenerative condition marked by the gradual degeneration of both upper and lower motor neurons, which causes muscle atrophy and ultimately respiratory failure [2]. Recent investigations indicate that ALS involves complex interactions among genetic mutations, protein aggregation, and neuroinflammation. However, different drugs have been used but effective treatments remain limited [3].

In recent years, nanotechnology has emerged as a transformative field with significant potential to revolutionize the diagnosis and treatment of neurodegenerative diseases. Defined by the manipulation of matter at the nanoscale (1 to 100 nanometers), nanotechnology offers novel tools and techniques to address key challenges in the detection, monitoring, and management of these complex disorders [4]. High surface area, tunable size, and improved permeability are just a few of the physicochemical properties of nanomaterials, including nanoparticles, nanotubes, liposomes, dendrimers, and quantum dots. Their smaller size, surface modification, and special interactions help nanomaterials to pass the blood-brain barrier (BBB), target diseased sites, and improve the efficacy of therapeutic and diagnostic instruments [5].

Nanotechnology enables the proactive identification of pathogenic markers linked with neurodegenerative diseases using advanced imaging and biosensing technologies. One such approach involves using antibodies attached to gold nanoparticles (AuNPs) and quantum dots that can selectively bind to amyloid-β (Aβ) plaques or tau proteins, which aids in high-resolution imaging alongside AD biomarkers [6]. The use of magnetic contrast agents in peripheral angiography magnetic resonance imaging (MRI) significantly increased the performance of MRI, allowing for more neurodegenerative changes to be detected early [7].

In the field of therapy, nanocarriers, including liposomes, dendrimers, and polymeric nanoparticles,

have shown effectiveness in facilitating drug delivery across the BBB, improving bioavailability, and minimizing systemic toxicity. Targeted delivery systems using ligands such as lactoferrin or transferrin can improve receptor-mediated transcytosis, so improving the therapy delivery accuracy [8]. Furthermore, Nanocarriers that deliver siRNA or CRISPR-Cas9 components to silence or fix disease-related genes are being studied for use in gene therapy [9]. Even with these positive changes, we are still in the early stages of using nanotechnology to treat neurodegenerative diseases in people. Preclinical studies and well-crafted clinical trials must rigorously address issues with biocompatibility, long-term toxicity, immune response, and scalability [10]. When it comes to central nervous system (CNS)-targeted nanomedicine, regulatory and ethical issues must also be carefully worked out. Nanomedicine can be safely used in neurological settings if ethical and legal problems are worked out [11].

The review examines contemporary clinical studies, technological limitations, safety issues, and future outlooks for the application of nanotechnology in personalized neuromedicine. Therefore, this review aims to examine the various applications of nanotechnology in the diagnosis, monitoring, and treatment of neurodegenerative illnesses, specifically AD, PD, and ALS, both presently and in the future.

Overview of Neurodegenerative Diseases

Neurodegenerative diseases consist of a diverse group of disorders that have in common a gradual loss of neuronal populations, that leads to cognitive, motor and behavioral changes, which affect hundreds of millions across the globe and are anticipated to nearly double in prevalence over the next 20 years as populations grow older [12], thus grows the need to develop different tools and materials to combat this growing issue.

AD overview

It's an acquired neurodegenerative disease that result in the deterioration of motor and cognitive functions and stands as the leading cause of dementia, its etiologic is diverse and complicated, which stems from the combination of different factors such as age and genetics, as such our current knowledge of AD and its different pathologies which include various hypotheses, for example, the cholinergic, amyloid tau protein and oxidative stress among many others [13]. However, it is worth mentioning that the pathogenesis of AD is commonly associated with the build-up and formation of amyloid-β plaques extracellularly and neurofibrillary tangles intracellularly [14]. The different pathogenesis hypotheses can be summarized in Figure 1. Before covering the tau protein hypothesis, it's worth mentioning the normal function of the tau protein, which is a microtubule-associated protein (MAP) that is present and expressed in neuronal cells, and it is responsible for stabilizing microtubules and facilitating axonal transport. In its normal form, tau undergoes controlled phosphorylation, which allows it to bind and release from microtubules as needed [15].

The Tau Protein Hypothesis

The tau hypothesis states that the abnormal hyperphosphorylation and aggregation of tau protein play a central role in the pathogenesis and progression of Alzheimer's disease (AD), independent of or in parallel with amyloid-β (Aβ) pathology, we will summarize the hypothesis in the following points:

Hyperphosphorylation and aggregation: In AD, tau becomes hyperphosphorylated at the serine and threonine residues, then the hyperphosphorylated tau protein has a reduced binding affinity to microtubules, which further disrupts axonal transport from the cell body to the dendrites. This abnormal tau detaches from microtubules, destabilizes them, and aggregates into paired helical filaments (PHFs), which assemble into neurofibrillary tangles (NFTs), which are a known pathological hallmark of AD [15,16]. Key points about Hyperphosphorylation and how it works are as follows: (1) Increased activity /over-activation of kinases such as GSK-3β and CDK5. (2) Decreased activity / under-activation of phosphatases such as PP2A. (3) Oxidative stress and Aβ (amyloid plaques) toxicity may exacerbate tau phosphorylation.

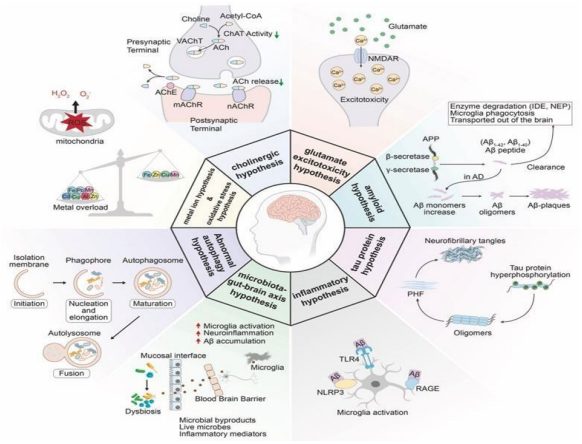

Figure 1. Different pathogenesis hypotheses of AD adapted from Zhang et al. [13]

Neurotoxicity of Tau aggregates: While mature NFTs were first believed to be the main toxic species, more evidence suggests that tau oligomers (smaller, soluble aggregates) are more neurotoxic than the final fibrillar tangles. These oligomers: (1) Disrupt synaptic function. (2) Damage mitochondrial function. (3) Induce inflammation. It's also worth mentioning that the misfolded tau protein spreads trans-synaptically, acting like a prion, changing and misfolding any normal tau protein it encounters, thus in this way the tau pathology is spread between brain regions [17,18].

Clinical and neuropathological relations: One of the models that is used for classifying the progression of Alzheimer's disease is the Braak staging system, which classifies based on the spread of misfolded tau proteins and the NFTs rather than amyloid plaques. Braak stages correlate more closely with cognitive deterioration than Aβ plaque buildup, suggesting tau pathology may be a more direct cause of neurodegeneration in AD [19,20]. Mechanisms of secretion and spreading of pathological tau protein are shown in Figure 2.

AD is subdivided into two diseases and can have different causes for it to arise and become pathological: 1-Familial Alzheimer's Disease (FAD) is a rare, hereditary form of Alzheimer's that arises from precise genetic mutations, which typically manifest at an earlier age compared to sporadic Alzheimer's disease. The predominant genes connected with FAD are comprised of the following genes: APP (amyloid precursor protein), PSEN1 (presenilin-1), and PSEN2

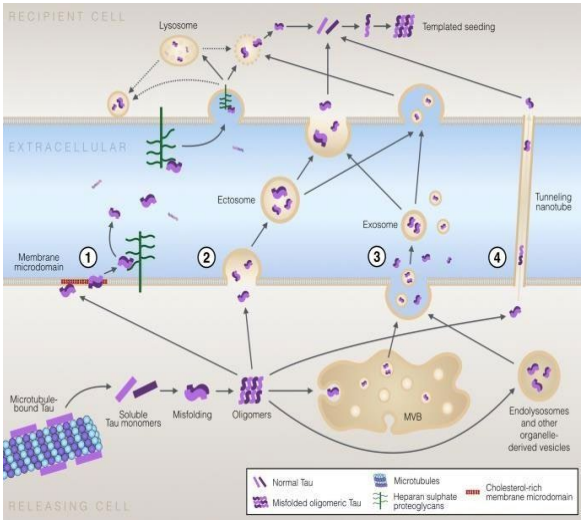

Figure 2. Mechanisms of secretion and spreading of pathological tau protein adapted from Brunello et al. [21].

(presenilin-2). Alterations in these genes lead to the unusual processing of amyloid precursor protein, resulting in the accumulation of beta-amyloid plaques, which are a known hallmark of Alzheimer's disease and pathology. Particularly, the mutations in the PSEN1 gene are mostly associated with early-onset Alzheimer's, often presenting symptoms in individuals ranging from 30 to 50 years old, while APP (amyloid precursor protein) mutations can also lead to aggressive disease progression [22]. 2- Sporadic Alzheimer's Disease (SAD): More than 97% of cases of Alzheimer's are caused by SAD and are mainly associated with aging, as the risk of developing the disease increases tremendously with age [23]. In contrast to Familial Alzheimer's disease (FAD), where genetic mutations are the main reason for the disease process, sporadic cases arise from an intricate interaction between genetic predispositions in individuals and environmental effects. The main etiologies of sporadic AD are still not fully understood, as the disease begins its onset from about 20 to 30 years before clinical symptoms begin to show up.

Previous research has shown a wide range of risk factors that can initiate and perpetuate the disease, with two main factors appearing: genetic and lifestyle risk factors. The most significant genetic risk factor for late-onset sporadic AD is the apolipoprotein E (ApoE), especially the E4 allele. Studies have shown that approximately 40-65% of individuals with AD carry the ApoE4 allele, which is linked with an increased risk of developing the disease [24]. On the other hand, the E2 allele seems to confer a protective effect, whereas the E3 allele shows no discernible influence [25]. Moreover, other studies have also shown the importance of the triggering receptor expressed on the myeloid cells 2 (TREM-2) gene; when it mutates, it leads to an increase in the individual's risk of developing AD by four times [26]. As well TREM-2 gene plays an important role in managing the immune system response within the central nervous system (CNS), emphasizing the potential connection between neuroinflammation and AD pathology [27].

Furthermore, genetic predispositions, lifestyle-related factors have risen as critical causes of sporadic AD. Different cardiovascular and metabolic conditions, including hypertension, diabetes type II, and a history of strokes, are identified as significant risk factors. Other aspects, such as chronic stress, substance abuse (including alcohol and tobacco), and an overall inactive and sedentary lifestyle, are believed to aggravate and speed up the disease process. The combination of these factors is believed

to engage biological pathways that may lead to the known hallmark features of AD, characterized by extracellular amyloid-β peptide accumulations and intracellular tau tangles and misfolds [28].

PD overview

Parkinson's Disease is well-known neurodegenerative disorder characterized by a gradual decline in motor function. It affects roughly about 1–2% of individuals over the age of 65 worldwide [29]. It was first medically described by James Parkinson, who described the symptoms as including resting tremors, bradykinesia, muscular rigidity, and postural abnormalities, seen in several patients [30]. These motor symptoms are the result of the deterioration of dopaminergic neurons, mainly in the substantia nigra pars compacta, which leads to a reduction in dopamine levels in the striatum, which is an area important for action planning and coordinating movement. As PD progresses, patients may also experience a range of non-motor symptoms, such as sleep disturbances, cognitive decline, depression, and autonomic dysfunction.

Pathologically, PD is distinguished by the presence of eosinophilic inclusions known as Lewy bodies, which are formed mainly by aggregation of misfolded protein α-synuclein (which exists normally in neuronal cells and helps in axonal transport), primarily within the surviving neurons of the substantia nigra and other key brain areas. This aggregation is linked with an impaired nigro-striatal system, resulting in motor deficits associated with the disease. Despite existing treatments, such as L-DOPA, which efficiently manage symptoms by improving dopamine levels, these interventions neither cure nor impede the disease's progression, but merely decrease its progression [31].

Further investigations into the main mechanisms of PD are important for the development of future therapies. Genetic discoveries regarding mutations in several genes, such as α-synuclein, parkin, and Leucine-rich repeat kinase 2, offer new insight into familial forms of PD, which have shown potential pathogenic pathways, implying that both familial and sporadic cases may share similar mechanisms. One of the hallmarks of (PD) is α-synuclein which is a normal protein found in neuronal cells and helps in facilitating axonal support but is at high risk of misfolding due to various factors such as oxidative stress mutations in specific genes and environmental conditions (exposure to heavy metals and /or pesticides for example) [31].

The Central role of α-Synuclein in the pathophysiology of Parkinson's disease is shown in Figure 3. Synaptic impairment and neurodegeneration arise through a series of events such as α-synuclein aggregation, deposition of oligomers and fibrils, formation of Lewy bodies understanding these changes that occur due to PD will draw a complete picture of the pathogenesis of PD and help in diagnosis and treatment [32,33] . Further molecular mechanisms contributing to Parkinson’s diseases is shown in Figure 4.

Lewy bodies are another hallmark of PD, and their pathological features are found in various neurodegenerative diseases, including Parkinson's disease and dementia with Lewy bodies (DLB). It's made up mostly of the protein alpha-synuclein (AS); these intraneuronal inclusions play a critical role in the pathogenesis of Lewy body diseases (LBD) [34]. The accumulation of AS and the formation of LBs are considered critical in neurodegenerative processes observed in these conditions. The aggregation of AS is followed by the disruption of cellular homeostasis, which leads to widespread mitochondrial dysfunction and disturbances in protein degradation pathways. Explicitly, the impairment of both the ubiquitin-proteasome system and the autophagy-lysosome pathway significantly contributes to neuronal death and toxic protein accumulation [35]. In PD, the formation of Lewy bodies usually occurs in specific regions of the brain, such as the brainstem and basal ganglia, and shows a relationship with the known hallmark motor symptoms of the disease. As the neurodegenerative process progresses, additional cortical involvement can lead to cognitive deterioration, which is characteristic of DLB.

Molecular studies suggest that the pathways leading to AS oligomerization involve alternative splicing mechanisms, which may influence the onset and progression of both PD and DLB [32,33]. Understanding the precise molecular interactions triggering AS aggregation is necessary for developing therapeutic techniques aimed at lessening the neurodegeneration associated with LBD. Efforts focused on targeting these molecular mechanisms may open a new way for new treatment options in the fight against Parkinson's disease and other related disorders. By describing the complex interplay between AS pathology, mitochondrial dysfunction, and the failure of protein degradation pathways. Parkinson's disease is divided into two types sporadic and familial which is summarized in Figure 5.

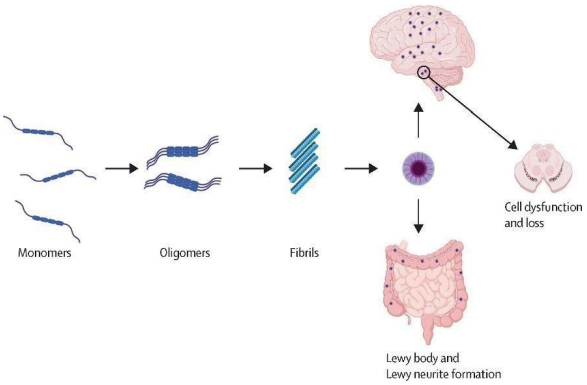

Figure 3. Central role of α-Synuclein in the pathophysiology of Parkinson's disease adapted from Morris et al. [31].

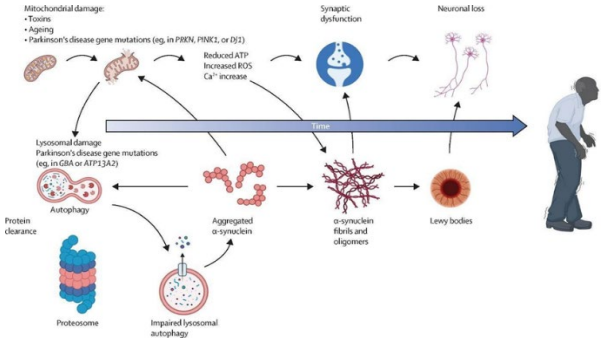

Figure 4. Molecular mechanisms contributing to Parkinson's disease adapted from Morris et al. [31].

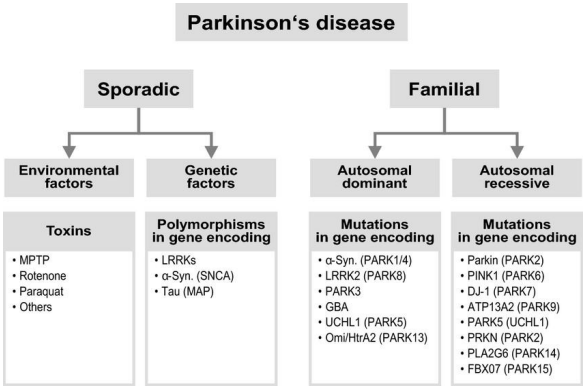

Figure 5. The comparison summarizes the sporadic and familial types of PD adapted from Jellinger et al. [41].

ALS overview

ALS is a progressive neurodegenerative disorder characterized by the deterioration of motor neurons in the cerebrum, brain stem, and spinal cord, leading to muscle weakness, atrophy, and paralysis. The disease usually begins showing symptoms in mid-adulthood, with a prognosis of 2 to 5 years post-diagnosis for most patients, and less than 10% survive more than [36].

The pathogenesis of ALS remains unknown [37], though it is recognized as a multifactorial process that involves both genetic and non-genetic factors. Around 5 to 10% of ALS cases are familial (FALS), with the remainder classified as sporadic cases. Significant genetic mutations attributed to ALS include those found in the superoxide dismutase 1 (SOD1) gene, the chromosome 9 open reading frame 72 (C9orf72), as well as fused in sarcoma (FUS) and TAR DNA-binding protein (TDP-43/TARDBP). These genetic mutations, particularly the C9orf72 hexanucleotide repeat expansion, have provided more information on the molecular mechanisms regarding motor neuron deterioration and the probable pathways involved in disease progression.

The loss of motor neurons is accompanied by an important involvement of glial cells, such as astrocytes and microglia, which contribute to the disease process through non-cell autonomous mechanisms. For instance, glial cells can secrete toxic substances, thereby exacerbating neuronal damage [38]. Furthermore, this toxicity can stem from various sources, including oxidative stress due to protein homeostasis imbalances, glutamate-mediated excitotoxicity due to the mutations in specific genes such as SOD1, the astrocyte's natural ability to get rid of excess glutamate begins to become faulty eventually leading to excitotoxicity, RNA metabolism disorders, and mitochondrial dysfunction. These findings highlight the complex interaction between neurons and their supportive glial cells in ALS pathogenesis, suggesting that therapeutic approaches that address both neuronal and glial contributions may be indispensable for the development of effective treatment strategies. However, several studies have shown that there is an unknown correlation between some types of heavy metals, like cadmium, that can affect individuals predisposed to having ALS. As such, further studies are required to dive into the effects of different heavy metals on ALS-predisposed individuals [39]

The pathophysiology of ALS is noted by the progressive deterioration of motor neurons located in the brain, brainstem, and spinal cord, which leads to severe muscle atrophy and eventually respiratory failure. While the exact mechanisms of ALS remain unknown, multifactorial elements contribute to its pathogenesis. Genetic factors play an important role, especially in familial cases, with mutations identified in genes such as superoxide dismutase 1 (SOD1), fused in sarcoma/translocated in liposarcoma, and TDP-43. The most prevalent genetic alteration in

familial ALS is a hexanucleotide repeat expansion in the C9orf72 gene. In sporadic forms of ALS, these genetic components are less defined; however, common pathways involving oxidative stress, mitochondrial dysfunction, and imbalances in protein homeostasis have been implicated across both sporadic and familial presentations. Apart from genetics, the involvement of non-cell autonomous mechanisms is important to understanding ALS pathophysiology.

Astrocytes and microglia have been identified as key factors contributing to the neurodegenerative process through inflammatory responses and the regulation of excitatory neurotransmission [38]. Increased levels of glutamate, an excitatory neurotransmitter, can lead to excitotoxicity, damaging motor neurons when not properly cleared by surrounding glial cells. [40] Furthermore, the accumulation of misfolded proteins can induce cellular stress in motor neurons, worsening their decline. Meanwhile, as oxidative stress continues to damage neuronal cells, a vicious cycle continues, sending the affected tissues into further dysregulation. In summary, the pathophysiology of ALS encompasses a complex interplay of genetic mutations, oxidative stress, improper excitatory signaling, and the role of glial cells, collectively working towards the neurodegeneration characteristic of this fatal disease. The pathophysiology of ALS and the different mechanisms that contribute to the disease is shown in Figure 6.

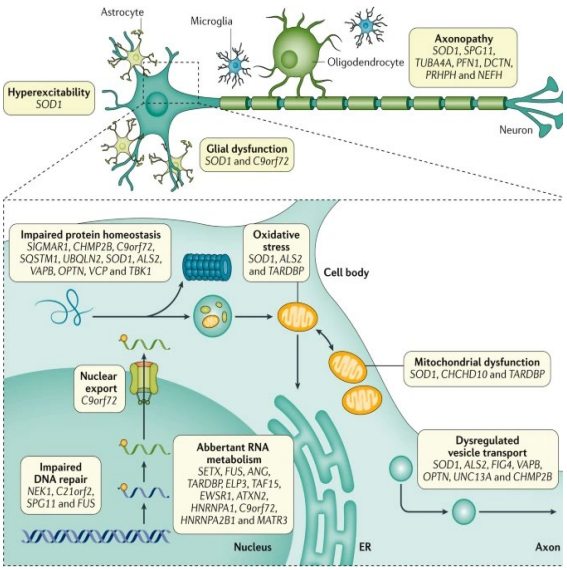

Figure 6. The pathogenesis mechanisms of ALS adapted from Hardiman et al. [42].

Role of Nanotechnology in Neurodegenerative Diseases

Neurodegenerative diseases and traumatic brain injuries represent significant global healthcare challenges, often resulting in irreversible neuronal damage and profound cognitive and motor dysfunction. Accurate and early diagnosis is critical for effective intervention, yet conventional diagnostic methods lack the sensitivity and specificity needed to detect early-stage neuronal changes. In this context, nanotechnology offers transformative potential. Nanoscale diagnostic tools such as nanoparticles, quantum dots, and nanobiosensors can cross the BBB and enable real-time, targeted detection of disease biomarkers at the molecular level. These technologies allow for highly sensitive imaging, early disease identification, and monitoring of disease progression, making them a powerful asset in the pursuit of precision diagnostics for neurodegenerative conditions. Precision medicine is gaining traction, and nanotechnology-based diagnostics are emerging as a key tool for improving clinical outcomes and patient care.

Nanotechnology in the AD diagnosis

Polymeric nanoparticles for Aβ plaques imaging

Studies have shown that targetable probes can cross the BBB using polysorbate 80-coated poly (butyl cyanoacrylate) dextran polymeric nanoparticles, facilitating the visualization of Aβ plaques in AD models [44]. Additionally, recent research indicates that sulfated dextran-coated iron oxide nanoparticles may enhance the bioimaging of microglia-induced brain inflammation through interactions with extensively expressed class A scavenger receptors. Fluorescence imaging has also employed rare-earth-doped nanoparticles, which bind to integrin αVβ3 and emit short-wave infrared light for improved imaging resolution [45].

Magnetic nanoparticles for Aβ plaque detection

Moreover, modified magnetic nanoparticles have been demonstrated to safely and effectively detect Aβ plaques in AD mouse models [46]. These researchers also noted that cholesterol levels are a critical biomarker for AD, and that higher levels can be effectively detected using anti-cholesterol antibody-conjugated magnetic nanoparticles. Furthermore, according to Sun et al. (2021), fluorescent nanoparticles can detect several Alzheimer's-related biomarkers, including tau proteins, inflammatory cytokines, and Aβ [47]. Collectively, these findings

suggest that nanoparticles offer a rapid and effective approach for identifying biomarkers associated with neurological disorders.

Nanotechnology in the PD Diagnosis
Photoelectrochemical using TiO_2 nanotube arrays for α-synuclein detection

α-Synuclein is a key neuronal protein closely associated with PD, and its quantitative detection typically requires sophisticated and time-consuming techniques such as nuclear magnetic resonance (NMR) spectroscopy, fluorescence measurements, western blotting, and size-exclusion chromatography. [48] developed a novel photoelectrochemical detection method using highly ordered, gold-doped TiO_2 nanotube arrays. These arrays served as effective platforms for immobilizing primary antibodies while maintaining their stability and binding affinity for α-synuclein. To enhance detection sensitivity, secondary antibodies were attached along with gold nanoparticle-conjugated glucose oxidase, enabling significant signal amplification. Glucose oxidase catalyzed the conversion of glucose into gluconic acid and hydrogen peroxide. When the opposite side of the titanium foil was irradiated, the resulting holes in the valence band of the nanotubes were scavenged by the generated hydrogen peroxide. This reaction produced a photocurrent proportional to the α-synuclein concentration, achieving detection levels in the picogram per milliliter (pg/mL) range [48].

Nanomaterial-based electrochemical biosensors for dopamine detection

Another important approach in the nano-diagnosis of PD involves the detection of dopamine levels, as the degeneration of dopaminergic neurons in the substantia nigra is a hallmark of PD. Recent studies have employed nanomaterial-based electrochemical biosensors for the sensitive and selective detection of dopamine in biological fluids. For instance, carbon-based nanomaterials such as graphene oxide and carbon nanotubes, often combined with metal nanoparticles like gold or platinum, have shown excellent conductivity, large surface area, and biocompatibility, which enhance sensor performance. These sensors can detect dopamine at nanomolar concentrations, making them promising tools for early-stage PD diagnosis. Furthermore, their portability and potential integration into point-of-care devices offer practical advantages for clinical applications [49,50]

Nanotechnology in the ALS Diagnosis
Magnetic nanoparticles in ALS imaging

Nanoparticles can enhance the resolution and sensitivity of imaging techniques used in ALS diagnosis and research. Magnetic nanoparticles, for instance, can be functionalized with imaging agents to improve the visualization of motor neurons and track disease progression. This enables better monitoring of therapeutic responses and the development of new imaging modalities for ALS [51].

Nanosensors for the detection of biomarkers in ALS

Nanotechnology-based sensors and platforms can aid in the early diagnosis and monitoring of ALS. Nanomaterials, such as quantum dots, gold nanoparticles, and any type of optical and photoluminescent active nanoparticles, can be used to detect specific biomarkers associated with ALS, such as neurofilament proteins or misfolded aggregates like TDP-43. These nanosensors enable sensitive and rapid detection of disease markers, facilitating early intervention and personalized treatment approaches [51].

Nanotechnology in Drug Delivery and Therapy

Neurodegenerative illnesses are managed lately using nanomaterials, which are being synthesized to overcome the minimal permeability to the BBB, as it's the main reason for failure of standard medication therapies' failure. Drugs, genes, or cells can be delivered via nanomaterials, and targeted specificity can be achieved by utilizing functionalized targeting ligands. In the aim of reducing the medication doses, controlled drug release can be accomplished via internal or external stimulation such as pH, temperature, magnetic field, Redox, and light, or by self-degradation. Furthermore, their loaded therapeutic agents are protected by nanocarriers, which also efficiently deliver them to inaccessible places like the brain [52,53]. Various classes of materials could be used to fabricate nanocarriers (e.g., polymers, ceramics, magnetic oxides, carbon, metals, albumin, lipids, and liposomes) [54]. Hence, nanocarriers have attracted a lot of interest recently in neurodegenerative diseases management.

Nano-therapy for AD management

Over the past five decades, liposomes have been extensively studied for their exceptional properties as drug delivery systems attributable to their structural composition. Liposomes are spherical vesicles including an internal aqueous core encased by a lipid bilayer; because of their characteristics, they are

regarded as nontoxic nanocarriers. Notably, they might protect the drug against enzymatic degradation, exhibit biocompatibility and biodegradability, demonstrate enhanced flexibility, and lack immunogenicity. [55,56]. For instance, the transferring (Tf)-functionalized liposomes demonstrated reasonable stability and encapsulation efficiency for less than two months. Additionally, the NPs sustained the release of the caffeic acid (CA) under physiologically mimicked conditions. Consequently, results demonstrate that Tf-functionalized liposomes loaded with CA may disassemble mature fibrils and inhibit Aβ aggregation and fibril generation [57].

For further targeted therapy, liposomes loaded with donepezil hydrochloride and tetradecyltriphenylphosphonium bromide were fabricated for enhancing penetration into the mitochondria of rat motoneurons; therefore, they improved learning and diminished the production of Aβ plaque in the hippocampus and entorhinal cortex [58] . In other words, the polymeric nanoparticles (pNPs) could be synthesized from natural raw materials such as alginate, chitosan, collagen, albumin, gelatin, fibrin, and gelatin. However, a variety of polymers are employed as precursors for formulating the synthetic pNPs, including PLGA (poly (lactic-co-glycolic acid)), PAMAM (poly(amido)amine), PLA (poly (lactic acid)), PEG (polyethylene glycol), PCL (polycaprolactone), and PGA (poly (glutamic acid) [59].

For example, Fucoxanthin-loaded PLGA-PEG nanoparticles demonstrated their capability of crossing the CNS additionally they reduced neurotoxicity in vitro by preventing the production of Aβ fibrils and oligomers. In mice with AD, intravenous administration of PLGA-PEG-Fuc nanoparticles lowered cognitive deficits, possibly through their action on the Nrf2 and NF-κB signaling pathways [60]. Moreover, RIV-loaded PLGA NPs formulations could effectively treat CNS disorders like AD. In-vivo brain cholinesterase estimation showed a reduction in brain cholinesterase activity compared to scopolamine-treated animals. This suggests RIV-loaded PLGA NPs are ideal carriers for delivering drugs to specific brain sites, potentially treating AD efficiently [61].

Nano-therapy for PD management

The distinctive features of metallic nanoparticles (MNPs) have made this class a trend in medical applications, in consequence of their uniform size and accurate size distribution. Their sizes range from 10 to 500 nm, thus enhancing their benefits over common pharmacological agents in noninvasive imaging and therapeutic delivery systems by enabling efficient interaction with biomolecules within cells [62,63]. Accordingly, they are used in PD treatment. For exemplify, AuNPs composites hindered PC12 cells and dopaminergic neurons programmed cell death and targeted certain cell types, which have shown a promising therapeutic benefit in managing PD by being able to pass across the BBB in the brains of mice [64].

Despite the versatile characteristics of MNPs, the lipid and polymeric based NPs are more favorable to be used due to its low toxicity [65], for example, Stearic acid and Brij 78 were used as lipids and surfactants to address PD symptoms, demonstrating over 80% encapsulation effectiveness and significant protection against reactive oxygen species [66] also, solid lipid nanoparticles (SLNs) combined with neurotoxic rotenone and GSE, can have antioxidant consequences in Parkinson's disease (PD) as the study found that DA/GSE-SLNs effectively protect against oxidative stress and rotenone-induced toxicity without affecting cell viability [67].

Additionally, polymeric nanoparticles in managing ND especially, PD are utilized due to their high Stability, biodegradability, and providing a sustainable drug release profile, easily functionalized NPS to enable their attachments to their suspected ligands and owing large drug loading and encapsulation capacity [68] thus, the biocompatible, non-immunogenic nature of albumin has enhanced the stability and half-life of an albumin-PLGA DA-loaded polymeric nanosystem then evaluated in a 6-OHDA-induced mouse model of PD, which their neurotherapeutic efficacy resulted in significant improvements in motor symptoms. compared with lesioned animals and those administered free L-Dopa [69,70].

Nano-therapy for ALS management

pNPs are used widely due to their biocompatibility, biodegradability, and enhancing drug stability [71,72]. For instance, FM19G11-based nano-therapies could delay the degeneration of muscles in ALS as well as other muscular diseases. Based on this, FM19G11-loaded nanoparticles significantly influence the bioenergetic status of G93A-SOD1 mouse myoblasts and enhance the transcriptional levels of key genes associated with mitochondrial activity, muscle differentiation, and cell proliferation. However, it also reduced mitochondrial networks and areas, indicating ROS elimination [73] . Also, mesoporous NPs are used

due to their biocompatibility, for example, A therapy cocktail (MSN-LEP-PIO) was introduced to TDP-43A315T mice to determine motor coordination and function. Body weight and motor coordination decreased, although the illness progressed more slowly and motor function increased; accordingly, the effectiveness of MSN-LEP-PIO in managing ALS is truly considerable [74].

Clinical Progress and Current Trials in Neurodegenerative Diseases

Neurodegenerative diseases are marked by progressive neuronal dysfunction and loss. While curative therapies remain elusive, recent clinical advancements and investigation trials are improving symptom control and offering hope for disease-modifying strategies.

Clinical progress and current trials in AD

In recent years, the future of AD treatment has begun to change, in part due to the development of new drugs. Among the most discussed of the updates is the F.D.A.'s accelerated approval of lecanemab, an antibody therapy that is supposed to help target and clear amyloid plaques. In Phase III trials, this treatment not only led to a clear reduction in amyloid levels apparent on brain scans but also provided a modest benefit in slowing cognitive decline, mainly in those diagnosed at a very early stage [75]. Another promising drug, donanemab, has also demonstrated promise in early symptomatic patients. Data from the TRAILBLAZER-ALZ 2 trial indicated a slower decline in terms of both cognition and daily function [76]. In the meantime, research is branching out from amyloid to target the tau protein, another AD hallmark. Aided by drugs including semorinemab and BIIB076, which are currently under clinical trial for preventing the brain from building up tau [77].

Beyond immunotherapies, researchers are also investigating neuroprotective drugs such as ALZ-801, a prodrug of tramiprosate. It does so by inhibiting the formation of toxic Aβ oligomers and is currently in late-stage trials [78]. Biomarker advances are also changing the way AD is diagnosed and followed up. Plasma markers, including the Aβ42/Aβ40 ratio and phosphorylated tau (p-tau217 and p-tau181), are starting to demonstrate utility for the earlier diagnosis of the disease earlier and selecting participants for clinical trials more effectively [79]. Together, these developments suggest a meaningful shift in Alzheimer's treatment from simply managing symptoms to targeting the root causes of the disease and potentially slowing its course.

Clinical progress and current trials in PD

For decades, treatments have mainly focused on managing symptoms, especially through medications like levodopa, which helps replenish dopamine, but these don't stop the disease from getting worse over time [80]. That said, the research field is shifting. Now, researchers are developing treatments to slow or even stop the disease process. One of these strategies is directly related to the α-synuclein protein. There is also some early optimism about a monoclonal antibody, called prasinezumab, which has recently completed Phase II trials and initial data suggest may aid in slowing the progression of motor symptoms [81].

Other strategies are repurposing drugs already used to treat other diseases. Ambroxol, a widely used cough medicine, for instance, is being tested in patients carrying mutations in the GBA gene. It does so by increasing the activity of a key enzyme involved in clearing cytotoxic waste, which could stave off the accumulation of α-synuclein [82]. Gene editing is also advancing. One treatment, VY-AADC, uses a gene to help the brain produce more dopamine. It is now in advanced clinical trials and gives hope in restoring motor function by upregulating dopamine synthesis in projected brain regions [83]. Cell therapy, however, is bolstering its case with the introduction of iPSCs. Those cells can then be transformed into dopamine-producing neurons and implanted in the brain. Early-phase clinical trials are underway to test this approach [84].

And technology is increasingly playing a role, too. Wearable devices and digital biomarkers are increasingly being employed in clinical trials for real-time, continuous monitoring of patients' movements and responses to treatments. Such information enables researchers to identify the fine-tuned therapies and to monitor the progress more precisely [85]. Overall, the field is progressing beyond just symptom management to attempting groundbreaking treatments with the potential to save brain function and change the course of the disease.

Clinical progress and current trials in PD

ALS is a devastating and ultimately fatal neurodegenerative disorder affecting the motor neurons that control skeletal muscle movement. With progression of the disease, muscle weakness,

atrophy, and then respiratory failure occur. While there are still few treatment options, there have been important steps forward in our understanding of ALS in the past few years, especially concerning its genetic basis.

Mutations in genes like SOD1, C9ORF72, and TARDBP are now recognized as key contributors to many inherited cases of the disease [86]. Among the most promising recent advances in studies of ALS is the use of small, synthetic strands of DNA or RNA, called antisense oligonucleotides (ASOs), that can alter how genes are expressed. One such, tofersen, is a targeted therapy which aims to reduce levels of the toxic SOD1 protein by targeting its mRNA. Clinical trials have shown that when tofersen is given early, it can reduce levels of neurofilament proteins as a sign of nerve damage and even help stabilize motor function in some patients [87]. The second novel strategy is cell therapy using stem cells. One of those, a therapy called NurOwn®, made it to Phase III tests. It is designed to release protective molecules called neurotrophic factors directly into the nervous system. To date, clinical results have been mixed and controversial, but the attempt demonstrates increasing interest in regenerative approaches [88, 89,90,91,92].

The potential contribution of neuroinflammatory processes to ALS is also being studied. Cancer drugs like ibrutinib, which manipulate the immune response, are being evaluated for the treatment of ALS [93]. In the meantime, gene therapy is progressing with approaches such as AAV vector-based delivery of small silencing RNA targeted at turning off the mutated genes implicated in the disease [94]. And just as important, the field is gaining on how ALS can be tracked. Biomarkers like neurofilament light chain (NfL) and phosphorylated neurofilament heavy chain (pNfH) have been increasingly considered as potential measures for disease progression, and a measure of responses to treatment in clinical trials [95]. Together, these advances have started to move the field toward more personalized and molecularly targeted therapies for ALS. There is still far to go, but the trajectory of current research offers new cause for optimism for better and safer medications [96].

Challenges and Limitations of Nanotechnology in Neurodegenerative Disease Treatment

BBB passing challenges

BBB poses an important challenge for the treatment of neurodegenerative diseases based on nanotechnology. BBB is composed of tightly packed endothelial cells, selectively controlling the movement of substances between blood and brain tissues and creating restrictions that prevent drug delivery to the central nervous system [97]. Due to the limitations of BBB, traditional drugs often have difficulty in obtaining sufficient concentrations in brain tissue, thus complicating the effectiveness of nanotechnology systems [98]. Complex BBB structures and active deposit mechanisms such as P-glycoproteins represent several obstacles that nanotechnology must overcome to ensure the effective delivery of drugs to neuronal targets [99]. Despite advances in nanocarrier design, maintaining reliable BBB penetration is an important challenge, as transport efficiency variability limits many nanomedicines therapeutic potentials [100].

Immunogenicity and inflammatory responses

Nanotechnology-based systems face significant challenges related to immune system recognition and inflammatory responses in applications for neurodegenerative diseases. When engineered nanoparticles are introduced into biological systems, they can provoke immune responses that diminish therapeutic efficacy and may exacerbate neuroinflammation [101]. These immunogenic reactions often result in the rapid clearance of nanocarriers from circulation, hindering their ability to reach target sites in the brain and reducing their therapeutic effectiveness [102]. The complex relationship between surface properties, sizes, and composition of nanoparticles affects immune recognition and complicates the design of a system that minimizes undesirable immune activation and preserves therapeutic functionality. Furthermore, the inflammatory microenvironment of neurodegenerative diseases can alter the immune response to nanomaterials, leading to unpredictable therapeutic results and potential safety concerns.

Neurotoxicity and safety concerns

Neurotoxicity is an important obstacle to the development of treatments based on nanotechnology for neurodegenerative diseases. Nanoparticles that can cross the brain barrier (BBB) are promising, but their accumulation in brain tissue can lead to direct cell damage and deterioration of normal neuronal function [103]. The feature of small size and surface reactivity that improves the effectiveness of nanoparticles in drug delivery can also increase toxicity [104]. The assessment of long-term safety regarding neurodegenerative disorders is

particularly complex because the progressive nature of these conditions complicates the distinction between neurodegeneration caused by disease and toxicity caused by nanoparticles. Furthermore, the lack of comprehensive toxicological data for many nanomaterials in neurological applications generates uncertainty regarding their long-term safety and impedes efforts to translate them into clinical applications.

Limitations of Targeting and Drug Delivery

Despite significant advances in nanotechnology, the achievement of specific targets and controlled delivery of drugs to certain regions of the brain remains a challenge in the treatment of neurodegenerative diseases. The diversity of these conditions exacerbates the development of a general strategy that effectively addresses different cell and molecular targets [105]. Current targeting methods often lack the specificity required to selectively deliver therapy agents to diseased neurons while saving healthy brain tissues, leading to suboptimal therapeutic results and potential side effects [106]. Furthermore, the dynamic microenvironment of the brain, characterized by changes in receptor expression and tissue architecture in neurodegenerative diseases, complicates targeting strategies and, over time, can reduce the effectiveness of nanoparticle-based delivery systems.

Biocompatibility and long-term stability issues

Biocompatibility and stability are important challenges to the treatment of neurodegenerative diseases using nanotechnology. The unique environment of the brain, including specific pH values, enzyme activity, and cell interactions, can influence the stability and efficacy of nanomaterials over time [102]. Many nanocarriers decompose and accumulate in body fluids, alter their targeting abilities and therapeutic efficacy, and cause harmful by-products [101]. Furthermore, it is not clear whether the long-term biocompatibility of brain nanomaterials is appropriate, and data on their fate, biodistribution, and potential accumulation in neuronal tissues are limited. These questions of stability and biocompatibility raise concerns about the long-term safety and efficacy of nanotechnology-based therapies for chronic neurodegenerative diseases.

Clinical translation challenges

Translating treatment based on nanotechnology from preclinical studies to clinical applications is a major challenge, especially in the field of neurodegenerative diseases. One of the main obstacles is the scale of manufacturing; many methods of synthesizing nanomaterials that work well in laboratory conditions are difficult to adapt to commercial production without compromising quality and consistency [102]. Moreover, the regulatory approval process for nanomedicine is complex and long, requiring a large amount of safety and efficacy data that may make it difficult to obtain brain therapy. High costs associated with the development and production of nanomedicines have created additional economic obstacles that can impede the application of these innovative treatments. In addition, the lack of standardization methods and quality control measures for nanomaterials in neurological applications complicates regulatory evaluation and approval processes.

Current research limitations and knowledge gaps

The understanding of nanotechnology applied to the treatment of neurodegenerative diseases has an immense gap. A limited understanding of the interactions between nanoparticles and brain cells affected by cancer hampers the development of more effective treatment strategies [104]. Current research is mainly focused on conceptual proof studies with limited long-term follow-up and unresolved questions about the sustainability and safety of nanomedicine interventions. The lack of standard animal models to reproduce human neurodegenerative diseases effectively complicates the translation of preliminary results into clinical applications. In addition, a lack of attention to patient heterogeneity and specific needs at different stages of the disease hinders the development of personalized methods of treatment of nanotechnology that can improve individual patient treatment outcomes.

Future Perspectives of Nanotechnology on Neurodegenerative Diseases

Nanotechnology holds considerable promise for revolutionizing the diagnosis, treatment, and monitoring of neurodegenerative diseases, such as AD, PD, and ALS. Given the complex pathophysiology of these disorders, including protein misfolding, oxidative stress, mitochondrial dysfunction, and BBB limitations, conventional therapies often fail to deliver drugs effectively or provide neuroprotection [107,108]. Nanotechnology-based systems, however, offer a multifaceted platform to overcome these limitations through targeted, controlled, and sustained delivery of therapeutics.

Precision targeting and personalized nanomedicine

Advances in ligand-conjugated NPs, such as those functionalized with antibodies, peptides, or aptamers, are enhancing the specificity of nanocarriers for disease-associated targets (e.g., amyloid-beta plaques, alpha-synuclein aggregates) [109,110]. In the future, integrating patient-specific biomarkers and genetic profiles into NP design could facilitate personalized nano-therapeutics, optimize efficacy and minimize off-target effects.

Multifunctional and theragnostic nanocarriers

The development of multifunctional nanoparticles that combine therapeutic and diagnostic capabilities, termed "theranostics," is expected to gain attention. These platforms can deliver neuroprotective agents while simultaneously enabling real-time imaging via magnetic resonance (e.g., superparamagnetic iron oxide nanoparticles) or fluorescence-based tracking [111,112]. Such systems will allow early diagnosis, disease monitoring, and feedback-driven treatment adjustments.

Crossing the BBB more effectively

Future nanocarriers will likely incorporate advanced strategies for trans-BBB delivery, including receptor-mediated transcytosis, cell-penetrating peptides, or even transient modulation of BBB permeability [113]. Stimuli-responsive systems triggered by pH, enzymes, or redox conditions are also being explored to release drugs selectively within affected brain regions.

Biodegradable and biocompatible nanomaterials

To ensure long-term safety, the development of biodegradable, non-toxic nanomaterials remain a key focus [114]. Natural polymers (e.g., chitosan, alginate, gelatin) and synthetic alternatives such as PLGA and PEGylated systems will continue to be optimized for reduced immunogenicity, efficient clearance, and minimal accumulation in non-target tissues [115].

Integration with advanced therapeutics

Nanotechnology will increasingly combine with advanced therapies such as gene therapy, RNA interference (RNAi), and CRISPR-Cas9 [116]. Nanocarriers can be engineered to protect nucleic acids from degradation and deliver them precisely to neural targets, opening new avenues for modifying neurodegerative disease progression at the molecular level.

Regulatory and translational challenges

Future research should emphasize vivo validation, standardized protocols, and human clinical trials to close the translational gap between laboratory and clinical application. Nevertheless, the use of natural polymers in nanobiocomposite formulations still presents certain difficulties. Large-scale production and reproducibility may be impacted by batch-to-batch irregularities, variability in physicochemical properties, and susceptibility to microbial contamination. Moreover, the stability of these nanocarriers under physiological conditions, together with their long-term toxicity, immunogenicity, and biodegradation profiles, require thorough investigation before clinical translation can be achieved.

CONCLUSION

Neurodegenerative diseases are characterized by the continuous decline of neuron function and cognitive abilities. Despite the presence of some approved drugs, they tend only to slow disease progression rather than treat the cause. Nanotechnology is a promising tool that can be used in both diagnosis and treatment. It provides potential diagnostic tools for neurodegenerative diseases by enabling sensitive detection of biomarkers through nanoscale biosensors and imaging probes that can identify diseases at early stages. In addition, the role of nanotechnology extends to therapy. Nanoparticles like liposomes, dendrimers, and polymeric carriers can cross the BBB, enhancing the effective drug accumulation in the brain. These types of nanoparticles not only enhance drug bioavailability but also help in controlling their potential toxicity. To evaluate this therapeutic potential, several studies have investigated the use of nanocarriers for drug encapsulation as a part of nanoparticle-based delivery systems, which succeeded in reducing proteins that contribute to the worsening of diseases like AD and ALS. On the contrary, other studies showed insignificant change, accounting for the need for further research. The application of nanotechnology in treating neurodegenerative disease is still facing many challenges, such as the complexity of diseases, limited early diagnosis capabilities that still require optimization, metabolism, and clearance from the target site after delivering the drug. Based on the foregoing, several studies and clinical trials need to be done prior to the

application of nanotechnology in the treatment of neurodegenerative diseases. Moreover, continued research is essential to fully understand the mechanisms and long-term safety of these nano-based interventions.

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