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NANOPARTICLE-BASED MODULATION OF NEURONAL ACTIVITY AND NEUROPROTECTION IN PARKINSON'S AND ALZHEIMER'S DISEASE

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Abstract

Parkinson's disease (PD) and Alzheimer's disease (AD) are diseases which affect more than 50 million people worldwide but there are no known disease modifying therapies. Small molecule drugs and virtually no biologics are able to cross the blood-brain barrier (BBB). The introduction of a platform technology that would cross the BBB and deliver neuroprotective agents in a controlled manner, along with modulation of neuronal activity through external physical stimuli like light or magnetic fields, has made nanoparticles a transformative solution. The current critical review deals with the use of nanoparticles in the context of neuroprotection and direct neuromodulation in PD and AD. The platforms that are neuroprotective are: antioxidant (cerium oxide); anti-aggregation (curcumin-PLGA, gold nanoparticles); anti-inflammatory (minocycline lipid nanoparticles); neurotrophic factor carrier (GDNF-PLGA, BDNF-chitosan); and gene therapy vectors (CRISPR-Cas9 lipid nanoparticles, siRNA-loaded exosomes). The different strategies of neuromodulation include photothermal (use of gold nanoparticles and near-infrared light), magnetothermal (use of iron oxide nanoparticles and alternating magnetic fields), ultrasound-sensitive nanodroplets, and nanoparticle-enhanced optogenetics. There is also a review of theranostic nanoparticles that combine MRI, fluorescence or PET with therapy. Preliminary findings in rodent models show a decrease in protein aggregation, oxidative stress, and neuroinflammation, as well as increased dopamine levels and enhanced motor and cognitive function. Subchronic study shows that biodegradable formulations are safe. The clinical translation is also in its early stages and includes ferumoxytol (MRI) and nanoliposomal curcumin (Phase I). This is set to evolve into customised targeting, closed-loop release and machine learning-based design in the future.

1. INTRODUCTION

1.1 Epidemiology and Pathological Hallmarks of Parkinson's and Alzheimer's Disease

Parkinson's is the second most common neurodegenerative condition, with around 1-2% of people over 65 years of age being diagnosed with the disease. The pathological feature of PD is the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), with the presence of Lewy bodies, protein aggregates in the cytoplasm, mainly composed of misfolded α-synuclein. The clinical picture is characterized by resting tremor, bradykinesia, rigidity and postural instability along with non-motor symptoms such as depression,

autonomic dysfunction, and cognitive impairment. In contrast, Alzheimer's disease accounts for about 10-15% of people over 65 years old, and is marked by extracellular amyloid-β plaques and intracellular neurofibrillary tangles (NFTs) of the hyperphosphorylated tau protein. In AD, the initial site of neurodegeneration is the entorhinal cortex and hippocampus, which are involved in memory formation, and progresses to neocortex. Although PD and AD are different proteinopathies, they have similar downstream mechanisms such as oxidative stress, compromised protein clearance through the ubiquitin-proteasome system and impaired autophagy, and neuroinflammation (Abdelmonem et al., 2024).

1.2 Current Limitations of Conventional Therapies

Levodopa is the gold standard treatment for PD, as it is a dopamine precursor that is taken up into the BBB through the large neutral amino acid transporter. Levodopa is effective in reducing motor symptoms, but has not been shown to slow disease progression, and can be complicated by motor fluctuations and levodopa-induced dyskinesia when used long term. Symptomatic treatment with dopamine agonists and/or monoamine oxidase B inhibitors is equally ineffective at altering underlying neurodegeneration (Akande, 2025). Cholinesterase inhibitors, like donepezil and rivastigmine, have modest, short-term cognitive benefits and memantine, an N-methyl-D-aspartate antagonist, is approved for moderate to severe disease. New anti-amyloid antibodies (aducanumab, lecanemab) have recently been FDA approved, but these biologic drugs are administered intravenously, have the potential for amyloid related imaging abnormalities and only help to stop clinical decline by about 10-20%. Most of these are poorly penetrating the brain, with of systemic administration only 0.1–2% reaching the brain parenchyma, critically (Ansari et al., 2024).

1.3 Why Nanoparticles for Neurodegenerative Disease?

Nanoparticles have some benefits that directly overcome the drawbacks of traditional therapies. First, nanoparticles between 10 and 200 nm can cross the BBB by several different mechanisms, the most prominent being when they are surface-conjugated to ligands such as transferrin, angiopep-2, and lactoferrin. Second, nanoparticles allow controlled and sustained release of the drug over days to weeks so that the dosage can be decreased and systemic side effects minimized. Third, the surface-to-volume ratio of nanoparticles is very high, permitting multifunctional design, such as targeting ligands, therapeutic cargo and imaging contrast agents being encapsulated within a single platform (Arora, Sharma, Layek, & Singh, 2021).

Fourth, some nanomaterials (e.g., gold, iron oxide) can convert external physical stimuli (light, magnetic fields) into local mechanical effects or local heat, allowing for the controlled modulation of neuronal activity without genetic manipulation. Fifth, nanoparticles will enable the protection of labile biomolecules such as nucleic acids (siRNA, mRNA, CRISPR components) and neurotrophic factors from enzymatic degradation. The properties have made nanobiotechnology a promising approach to neuroprotection and neuromodulation of PD and AD (Ashraf, Solla, & Sechi, 2022).

2. Nanoparticle-Mediated Blood-Brain Barrier Crossing

2.1 Anatomy of the Blood-Brain Barrier and Transport Pathways

The BBB is a highly selective neurovascular unit, consisting of brain microvascular endothelial cells, pericytes, astrocytes and the underlying basement membrane. These endothelial cells are linked together by continuous tight junctions that consist of claudins, occludins and junctional adhesion molecules, which prevent the paracellular movement of solutes of more than ~500 Daltons. Moreover, efflux transporters like P-glycoprotein and breast cancer resistance protein actively expel a diverse range of lipophilic drugs from the CNS back into the blood, thus further restricting brain

penetration (Awad et al., 2025). The BBB allows the passage of only small lipophilic molecules (such as caffeine, nicotine, and essential nutrients like glucose, amino-acids, iron, and insulin) by specific transporters or receptor-mediated processes under physiological conditions. This very strong barrier, although necessary for keeping brain home-stable, is the biggest hurdle in the way of developing therapies for neurodegenerative diseases. Nanoparticles have been developed to take advantage of these receptor-mediated transport pathways to achieve therapeutic levels in the brain without damaging the integrity of the tight junctions (Babalola et al., 2025).

2.2 Receptor-Mediated Transcytosis

The best validated method for delivering nanoparticles across the BBB is by receptor-mediated transcytosis. It requires binding of a nanoparticle conjugated ligand to its cognate receptor on the luminal surface of brain endothelial cells, subsequent clathrin-mediated endocytosis, transportation through the cytoplasm and exocytosis on the abluminal side into the brain parenchyma (Rashad, 2025). The most universal target exploited is the transferrin receptor which is highly expressed on brain endothelial cells and is constitutively recycled. Several types of transferrin-conjugated nanoparticles such as PLGA, liposomal and polymeric nanoparticles have been demonstrated to selectively uptake into the brain for delivery of neurotrophic factors (GDNF, BDNF), small molecules (curcumin, resveratrol) and nucleic acids (siRNA, plasmid DNA) with up to 10-20-fold higher concentrations than non-targeted controls (Bahadorani, Nasiri, Dellinger, Aravamudhan, & Zadegan, 2024).

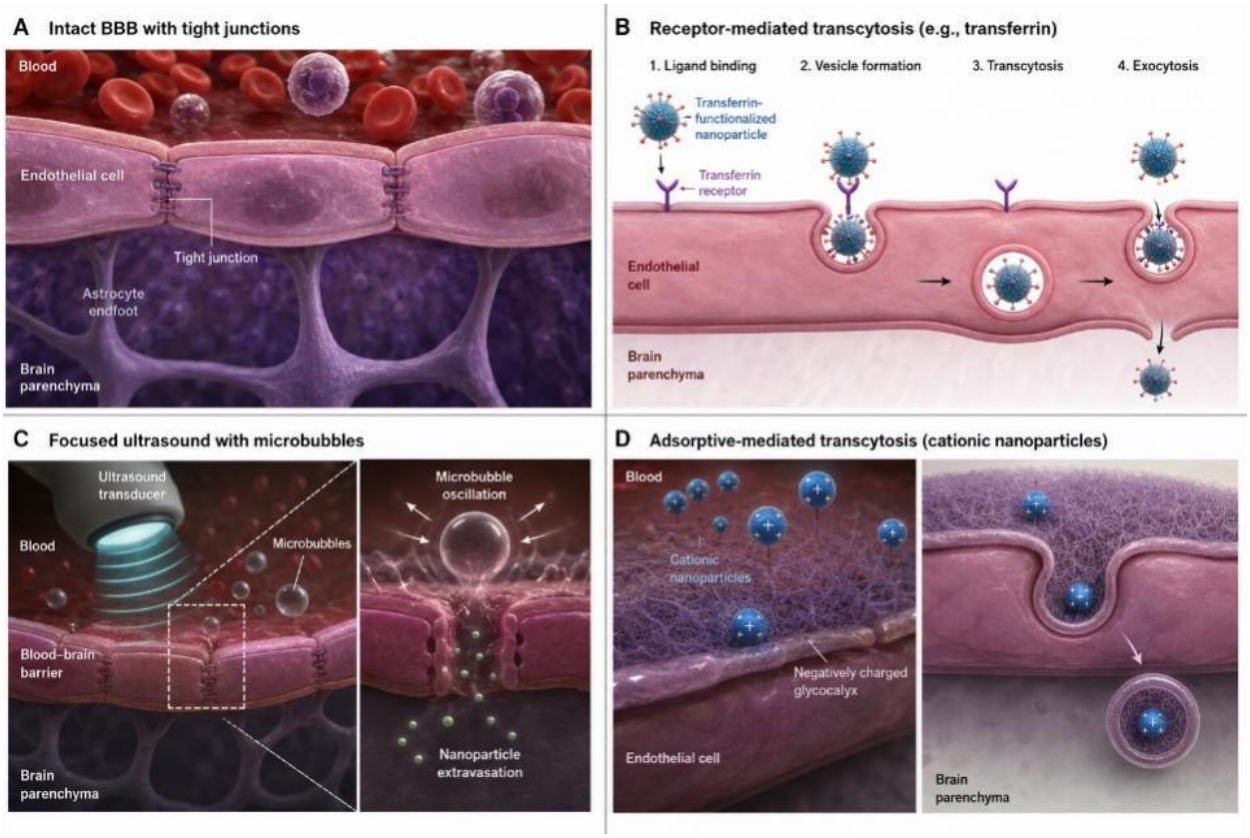
Transferrin targeted PLGA nanoparticles for delivery of GDNF, for instance, have shown sustained striatal levels of GDNF for 28 days post single intravenous administration in rats, which resulted in considerable preservation of tyrosine hydroxylase-positive neurons in the 6-hydroxydopamine model of PD (Balkrishna et al., 2024) .

Another promising target is the LDL receptor related protein 1 (LRP1) in general, and the peptide ligand angiopep-2 in particular. In some studies, angiopep-2–conjugated nanoparticles have been shown to penetrate the BBB more effectively than transferrin-based systems, which may be explained by the higher expression of LRP1 on endothelial cells and on neurons. On the other hand, following four weekly intravenous injections, curcumin loaded angiopep-2 liposomes reduced amyloid-β plaque burden by about 60% and at the same time improved the performance of the APP/PS1 mice in the Morris water maze (Rai, 2024). The rabies virus glycoprotein-derived peptide RVG29 targets the nicotinic acetylcholine receptor on brain endothelial cells, and has been successfully used to deliver siRNA against α-synuclein with protein aggregates reduced by 60% in the A53T mouse model of PD (Balkrishna et al., 2024). Lactoferrin is an iron-binding glycoprotein that binds to LRP1, which was used on chitosan nanoparticles and shown to deliver resveratrol into the hippocampus, causing a decrease in amyloid-β levels and an increase in cognitive function in aged rats.

The most validated ligands targeting BBB for drug delivery, the receptors which they bind, the nanoparticle formulations, the therapeutic cargoes and the disease models are summarized in Table 1, each with quantitative efficacy measures. Examples of the formulated nanoparticles are transferrin-PLGA nanoparticles for GDNF delivery in PD rats (70% preservation of tyrosine hydroxylase neurons), angiopep-2 liposomes for curcumin in AD mice (65% plaque reduction), RVG29-exosomes for siRNA against α-synuclein in PD mice (60% reduction in aggregates), and lactoferrin-chitosan nanoparticles for resveratrol in AD rats (improved Morris water maze performance). In all of these investigations, a one to two order-of-magnitude higher accumulation in the brain has been observed with receptor mediated targeting than without it for nanoparticles (Barbaro, 2024).

Table 1: *Summary of BBB-targeting ligands, receptors, and nanoparticle formulations validated in PD/AD models.*

Ligand	Receptor	Nanoparticle Type	Cargo	Disease Model
Transferrin	TfR	PLGA-PEG	GDNF	PD (rat)
Angiopep-2	LRP1	Liposome	Curcumin	AD (mouse)
RVG29 (rabies virus)	nAChR	Exosome-mimetic	siRNA (α-syn)	PD (mouse)
Lactoferrin	LRP1	Chitosan	Resveratrol	AD (rat)



The mechanisms of crossing the blood-brain barrier with nanoparticles. Figure 1 shows schematic representation of the intact blood-brain barrier with brain microvascular endothelial cells with tight junctions (claudin-5, occludin, ZO-1), surrounded by pericytes embedded in the basement membrane and astrocytic end-feet. Receptor-mediated transcytosis: A ligand-conjugated NP (e.g., transferrin-NP) binds to its cognate receptor (e.g., transferrin receptor) on the luminal membrane of the endothelial cell, is endocytosed into the cell by clathrin, is transported through the cytoplasm in a clathrin-containing vesicle, and is exocytosed on the abluminal side into the brain parenchyma. The transcellular route is enabled by (C) focused ultrasound-assisted BBB opening, which involves the use of intravenously injected microbubbles (1–

10 μm) to create mechanical forces through their oscillation when stimulated by focused ultrasound pulses to transiently break tight junctions and allow paracellular diffusion of nanoparticles. (D) Adsorptive-mediated transcytosis: Cationic nanoparticles (positively charged) electrostatically bind to the glycocalyx on the luminal endothelial membrane, resulting in non-specific endocytosis and transcytosis (Baruah, 2025).

Figure 1: *(A) Intact BBB barrier. (B) Receptor-mediated transcytosis via ligand–receptor binding. (C) Focused ultrasound + microbubbles transiently open BBB. (D) Adsorptive-mediated transport via electrostatic interaction of cationic nanoparticles with endothelium.*

2.3 Focused Ultrasound-Assisted Blood-Brain Barrier Opening

Other approaches that are not based on receptor mediated uptake are focused ultrasound combined with intravenous microbubbles, which transiently and reversibly disrupts tight junctions. With focused ultrasound pulses, microbubbles (1–10 micrometers in diameter) undergo oscillations and generate mechanical forces, which push against endothelial cell membranes, temporarily opening tight junctions and allowing nanoparticles and even larger therapeutics to spread into the brain parenchyma. Tight junctions reseal spontaneously once the BBB is disrupted by sonication, the initial phase of which lasts about 4–6 hours. Such strategy has been applied to improve delivery of different types of nanoparticles such as liposomes, polymeric nanoparticles and even antibody-drug conjugates, to achieve brain accumulation improving by 10- to 50-fold (Baruah & Kalita, 2025).

Focused ultrasound in conjunction with GDNF loaded PLGA nanoparticles led to better behavioural recovery and preservation of dopaminergic neurons than PLGA nanoparticles alone for the purposes of PD. For the anti-amyloid antibody treatment, focused ultrasound has been used in AD models to deliver anti-amyloid antibody, where improved plaques clearance and decreased neuroinflammation were observed (Benjamin, Júnior, Dutra, & de Andrade). The key benefit of focused ultrasound is that it is noninvasive and can be directed with millimetre precision to specific brain regions (e.g. substantia nigra in PD, hippocampus in AD). There are, however, some concerns regarding the possible occurrence of microhemorrhages, possible neuroinflammation that can result from multiple sonications, and the requirement for specialized equipment that is not readily available (Bernatoniene, Plieskis, & Petrikonis, 2025).

2.4 Cell-Mediated Delivery Using Macrophages and Exosomes

The natural tendency of some cell types to home to inflammatory or diseased tissues is the basis of cell-based delivery systems. For instance, macrophages infiltrate areas of neuroinflammation in PD and AD, crossing the BBB by diapedesis. The researchers have now been able to target specific regions of the brain, which have active microglial activation, by loading macrophages with drug-containing nanoparticles ex vivo, and then reinfusing them. Primary macrophages were engulfed with iron oxide nanoparticles to carry the anti-inflammatory agent minocycline and then injected into MPTP treated mice (Bhattacharya, Mukherjee, Kayal, & Saha). The macrophages moved to the substantia nigra where they released the nanoparticles, leading to less microglial activation and maintenance of dopaminergic neurons than free drug and untargeted nanoparticles (Bhaskar et al., 2024).

Another of the cell-derived nanoparticle platforms that possess an inherent ability to cross the BBB are the naturally secreted extracellular vesicles, called exosomes, with a diameter of 30–150 nm. Exosomes are engineered to express surface proteins (CD47, tetraspanins) that reduce opsonization and increase the circulation time, and can be engineered to express targeting ligands or loaded with therapeutic cargoes (Bogadi et al., 2025). The catalase mRNA-loaded RVG29-modified exosomes decreased the oxidative stress and successfully protected the dopaminergic neurons in the PD mouse model. Likewise, anti-inflammatory microRNAs and growth factors, which are inherent properties of exosomes produced by the MSC, also have a neuroprotective effect, and BACE1-siRNA loaded exosomes were

able to inhibit the production of Aβ in AD mice. Exosomes possess several key features that make them highly attractive for therapeutic applications: they are low-immunogenic and they can cross the BBB without the need for targeting ligands, albeit producing them on a large scale, standardizing them and loading them with therapeutic cargoes remains a challenge (Brito et al., 2025).

3. Nanoparticles for Neuroprotection in Parkinson's and Alzheimer's Disease

3.1 Anti-Oxidant Nanoparticles

Oxidative stress is a common pathogenic pathway in PD and AD, characterized by increased production of the molecules that are produced when oxygen is oxidized, such as superoxide anion, hydrogen peroxide and hydroxyl radicals, and decreased functionality of the endogenous antioxidant defenses. This is especially problematic for dopaminergic neurons in the substantia nigra, as they are particularly vulnerable to being poisoned by the hydrogen peroxide they create during dopamine metabolism, and the high iron content of this area fosters fenton chemistry.

In a similar manner, in AD, amyloid-β oligomers cause mitochondrial dysfunction and production of Reactive Oxygen Species. Nanoceria, or CeO_2 nanoparticles, have been the subject of much research owing to the presence of both Ce^{3+} and Ce^{4+} surface oxidation states, which gives them catalase-mimetic and superoxide dismutase-mimetic activities (Chengebroyen et al., 2025). The oxygen vacancies in the cerium oxide lattice allow a continuous cycle between Ce3+ and Ce4+ that enables these nanoparticles to catalyze multiple reactive oxygen species instead of reacting with them in a stoichiometric way (Rai, 2024).

Using primary cortical neurons cultured in the presence of hydrogen peroxide or amyloid-β oligomers, in vitro studies showed that cerium oxide nanoparticles (5–10 nanometers, PEGylated for stability) decreased the level of intracellular ROS by ~80% and blocked neuronal apoptosis as evidenced by decreased caspase-3 activation and TUNEL staining. This protective effect was concentration-dependent and was found to be optimal at 10–100 micrograms/mL. Twenty mice suffering from PD in the mouse model of MPTP were treated with PEGylated cerium oxide nanoparticles (5 mg/kg, twice a week for 4 weeks) which resulted in a 60% loss of tyrosine hydroxylase-positive neurons in the substantia nigra of the untreated mouse, versus a loss of only 20% in the treated mouse. In addition, the microglial activation, measured by the Iba-1 immunohistochemistry and CD68 expression was significantly reduced in the group treated with nanoparticles, indicating the antioxidant activity also has an anti-inflammatory effect (Chepuri et al., 2025).

Intraperitoneal injection of cerium oxide nanoparticles at the same dose was found to decrease the amount of amyloid-β plaques in the hippocampus and cortex by about 50% as observed by thioflavin-S staining and enzyme-linked immunosorbent assay in APP/PS1 mice. This effect is most likely indirect; cerium oxide nanoparticles do not directly bind to amyloid-β, but instead decrease oxidative stress that has been found to drive amyloid-β aggregation and to stabilize amyloid-β oligomers. Importantly, no overt toxicity was seen in any of these studies, and liver and kidney function tests were within normal range, while there was no evidence of neuronal damage in any of the control brain regions (P Chokkalingam, 2025).

Other antioxidant nanoparticles are ceria-zirconia solid solutions with a higher oxygen storage capacity, and manganese oxide nanoparticles that act like superoxide dismutase. Currently, cerium oxide is the most fully characterized and is being investigated in a Phase I clinical trial for radiation-induced brain injury; this could lead to clinical trials in neurodegenerative diseases (Parthiban Chokkalingam, Bera, Das, Saito, & Das, 2025).

3.2 Anti-Aggregation Nanoparticles

Pathological aggregation of α-synuclein in PD and amyloid-β in AD is an important therapeutic target because it is believed that the oligomeric intermediates are the most neurotoxic species. The polyphenolic compound curcumin is also known to inhibit the α-synuclein dimerization and amyloid-β fibrillogenesis, to destabilize pre-formed fibrils and to decrease the cytotoxicity of oligomers (de Moura, 2024). The curcumins, however, have

very low water solubility and bioavailability, and less than 1% of an oral dose is absorbed into systemic circulation. Curcumin is highly encapsulated with poly(lactic-co-glycolic acid) (PLGA) nanoparticles, which significantly enhance its solubility, stability and brain delivery. PLGA nanoparticles loaded with curcumin were synthesized by the single-emulsion, solvent evaporation method with approximate diameter of 120 nm, with less than 0.2 polydispersity index and more than 85% of nanoparticles loaded with curcumin. In vitro, the nanoparticles were found to inhibit the amyloid-β (1-42) fibrillization by 90% at 5 micromolar of curcumin when measured by thioflavin T (Thio-T) fluorescent readout (Dipankar, Salazar, Dennard, Mohiyuddin, & Nguyen, 2025).

The untreated amyloid-β samples, after 7 days of incubation, showed long, branched fibrils, whereas the samples treated with curcumin loaded PLGA nanoparticles exhibited only small, amorphous aggregates (Küpeli Akkol et al., 2022). The nanoparticles also fragmented preformed fibrils, with a 60% decrease in thioflavin T fluorescence after 24 hours of treatment. Immunohistochemistry with the 6E10 antibody showed that the hippocampal amyloid-β (Aβ) plaque burden was 65% reduced in APP/PS1 transgenic mice that had received intravenously injected transferrin-targeted curcuminPLGA nanoparticles (2 mg/kg of curcumin equivalent twice weekly for 4 weeks) compared to control mice. This showed that curcumin alone at the same dose did not yield any significant effect, underscoring the need for nanoparticle encapsulation (Ferreira, 2021).

Curcumin is also able to inhibit α-synuclein aggregation in PD when loaded into PLGA nanoparticles. Intravenous injection of these nanoparticles decreased the density of α-synuclein-positive aggregates in the substantia nigra by ~70% and motor function on the rotarod and pole tests in the A53T transgenic mice expressing human mutant α-synuclein. Dopamine-functionalized gold nanoparticles (NPs) also have been found to inhibit α-synuclein fibrillation. It works by the binding of dopamine-functionalized gold nanoparticles to the non-amyloid-β component region of α-synuclein that stabilizes the monomeric form and prevents nucleation (Girigoswami, Pallavi, & Girigoswami, 2023). When the PD model was made using a Caenorhabditis elegans strain expressing human α-synuclein in muscle cells, dopamine-functionalized gold nanoparticles, at 1 nM concentration, resulted in an 80% decrease in the number of aggregates, and an improvement in worm motility (Saunier, 2021). Beyond being antioxidants, cerium oxide nanoparticles have been found to disaggregate amyloid-β and α-synuclein fibrils as well, possibly by surface-mediated interactions which disrupt the cross-beta sheet structure. All these studies have shown that anti-aggregation nanoparticles can target multiple pathogenic proteins and can also combat oxidative stress (Gomes, Ramalho, Loureiro, & Pereira, 2025).

As figure 2 shows the inhibition of protein aggregation by the use of nanoparticles. The fluorescence assay results of the Panel A, which uses thioflavin T, indicate that the amyloid-β (1-42) fibrillization process is strongly inhibited by curcumin-PLGA nanoparticles (100 nM curcumin equivalent), while the free curcumin at the same concentration only inhibits the fibrillization process by 20% because of aggregation and precipitation. The images are from the transmission electron microscopy (TEM) of the untreated amyloid-β samples, which appear as long, branching fibrils (scale bar 200 nanometers), and from the curcumin-PLGA nanoparticle treated samples, which consist only of small amorphous aggregates. Immunohistochemistry results of APP/PS1 mouse hippocampus stained with 6E10 antibody against amyloid-β is presented in panel C: The 65% reduction in plaque area ($p<0.001$ vs. untreated) in the 6E10 immunoreactivity in the hippocampus of the nanoparticle treated group is shown as a quantitative bar graph.

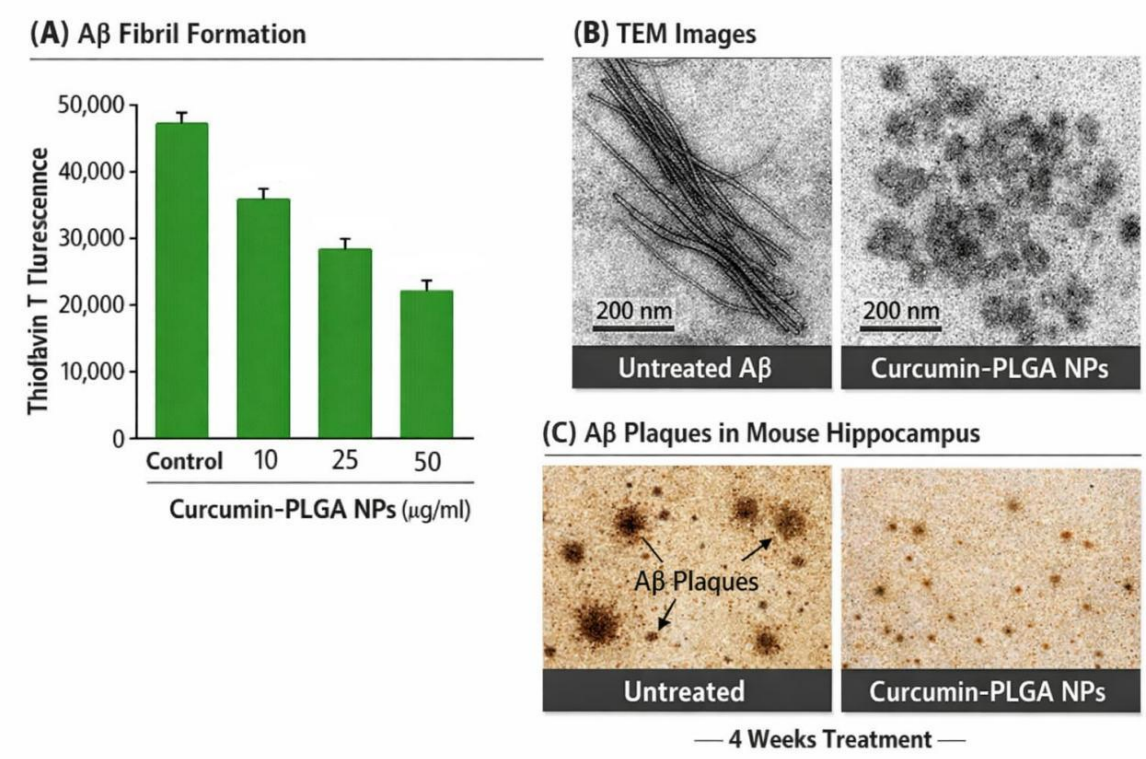


Figure 2: ***Nanoparticle-mediated inhibition of amyloid-β (Aβ) aggregation and plaque formation***

3.3 Anti-Inflammatory Nanoparticles

In both PD and AD, chronic neuroinflammation is caused by activation of microglia and astrocytes that trigger neurodegeneration. When microglia are activated, they produce pro-inflammatory cytokines, such as Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1 beta (IL-1β), and Interleukin-6, in addition to Reactive Oxygen Species and nitric oxide, due to aggregated proteins and Damage Associated Molecular Patterns (DAMPs). Microglia are initially neuroprotective but if they are persistently activated, they lead to neuronal death. Minocycline is a semi-synthetic tetracycline used for its potent anti-inflammatory/anti-apoptotic properties, which do not translate into antimicrobial activity, but has low brain penetration (brain-to-plasma ratio ~0.3) and high systemic doses are needed. Brain delivery of minocycline is enhanced by inclusion in lipid nanoparticles that reduce side effects; solid lipid nanoparticles and nanostructured lipid carriers (Goyal, Singh, Solanki, & Verma, 2025).

MPTP treated mice were prepared with minocycline loaded nanostructured lipid carriers (approximately 150 nanometers in size and zeta potential of –30 millivolts) administered intravenously in the mice (2.5 milligrams per kilogram minocycline equivalent, 3 times a week for 3 weeks). The microglial activation (Iba-1 immunoreactivity and CD68 expression) was 60% lower in the substantia nigra with the nanoparticle formulation (at the same dose) than with free minocycline. The amounts of TNF-α and IL-1β in the striatum, measured by enzyme-linked immunosorbent assay, were decreased by 70% and 65%, respectively, in the MPTP-treated mice compared to non-treated MPTP mice. Most importantly, the number of tyrosine hydroxylase positive neurons in the substantia nigra was maintained by 75% in the nanoparticle group vs 30% in the free minocycline group, showing a direct correlation of increased brain delivery to neuroprotection (Gupta, Kumar, Gupta, Kumar, & Kumar, 2025). The anti-inflammatory and anti-oxidative properties of a natural polyphenol,

resveratrol, have also been combined with nanoparticles. Intranasal administration of resveratrol-loaded chitosan nanoparticles for 200 micrograms per day for 4 weeks to aged rats (200 μ/day for 4 w) led to a decrease in microglial activation in the hippocampus and a switch from the pro-inflammatory M1 phenotype (characterized by the expression of TNF-α and inducible nitric oxide synthase) to the anti-inflammatory M2 phenotype (characterized by the expression of arginase-1 and IL-10). This phenotypic change was correlated with a positive effect on the performances of the novel object recognition and Morris water maze tests (Guzman-Lopez et al., 2022).

One very innovative method involves targeting microglia-specific nanoparticles. Anti-inflammatory cytokine IL-4 was delivered to the brains of APP/PS1 mice by using polymeric nanoparticles surface-functionalized with mannose, a ligand of the mannose receptor CD206 that is upregulated on activated microglia (Hou, Chen, Yang, & Lee, 2025). The administration of these mannose-targeted nanoparticles (intravenously once a week for eight weeks) decreased the level of amyloid-β plaque by 55% and improved cognitive function; the effects were believed to be due to the enhanced phagocytosis of amyloid-β by microglial cells. A promising point of interest for both PD and AD is the ability to repolarize microglia from a neurotoxic to a neuroprotective state by delivering immunomodulators to them using nanoparticles (Inamdar, Gurupadayya, Halagali, S, et al., 2024).

3.4 Neurotrophic Factor Delivery

The polypeptides used to promote the survival, differentiation and function of the neurons are called as neurotrophic factors. The most potent survival factor for dopaminergic neurons is glial cell line-derived neurotrophic factor, which has been a long sought-after goal for PD therapy. Nevertheless, GDNF is a large protein (Mw ~ 30 kD) that is not able to cross the BBB, and direct intracerebral infusion with implanted catheters did not reach the clinical trial stage, because of its limited distribution and off-target effects (Inamdar, Gurupadayya, Halagali, Tippavajhala, et al., 2024). Systemic administration of GDNF can result in sustained, wide-spread delivery via the use of nanoparticle encapsulation (A. Sharma, Tiwari, Sharma, Pathak, & Khan, 2025). The size of the PLGA nanoparticles is around 140 nanometers and the loading efficiency is 80 micrograms of GDNF per 1mg of PLGA nanoparticles, which were injected into the rats with unilateral 6-hydroxydopamine lesions of the medial forebrain bundle, a model of PD. The amount of GDNF, measured by enzyme-linked immunosorbent assay of brain homogenates, was detectable for 28 days after a single injection into the striatum. Treatment was evaluated by the behavioral recovery using amphetamine-induced rotation: the untreated lesion rats showed about 10 rotations per minute, but the rats treated with GDNF nanoparticles showed 2 rotations per minute similar to the sham-operated rats (R. Sharma et al., 2024). Nanoparticle-treated animals showed 70 percent preservation of tyrosine hydroxylase-positive neuron numbers in the substantia nigra, and 75 percent of the dopamine level in the striata was restored by HPLC. At the same dose, free GDNF did not work and non-targeted GDNF nanoparticles resulted in only modest (20%) neuronal preservation, indicating the importance of BBB targeting (Jadeja, Dudhat, & Prajapati, 2025).

In AD, the degeneration of cholinergic neurons in the basal forebrain is counteracted by brain derived neurotrophic factor. Cognitive impaired aged rats were intracranially injected with BDNF-chitosan nanoparticles (≈200nm) via the nose. The intranasal route avoids the BBB by following the olfactory and trigeminal nerve to the brain parenchyma. The BDNF level in the hippocampus rose by three times after 4 weeks of daily administration (200 micrograms BDNF equivalent per day) when compared to free BDNF (Jadeja et al., 2025). The rats treated with the nanoparticles demonstrated significantly better results in the Morris water maze tests as escape latency was reduced and the rats spent more time in the target quadrant. Levels of the synaptic proteins (both synaptophysin and PSD95) were near normal while levels of hippocampal neurogenesis (doublecortin immunostaining)

were raised by 80% over age-matched rats without treatment. No negative side effects like weight loss or behavioural abnormalities were noticed (Jagaran & Singh, 2021).

One newer method is to deliver lipid nanoparticles with mRNA coding for the neurotrophic factors akin to the mRNA vaccines for COVID-19. The GDNF mRNA-loaded lipid nanoparticles were intrathecally injected into 6-OHDA lesioned rats. This one injection produced GDNF protein for 14 days in the spinal cord and brain, and the number of dopaminergic neurons remained 65% of normal, while the level of motor function was greatly restored. With this platform it is possible to express the neurotrophic factor in a transient and controlled way, without the adverse effects of chronic overexpression as reported in some clinical trials (Kaitsuka, Matsushita, & Matsushita, 2021).

3.5 Gene Therapy Nanoparticles for CRISPR and siRNA

The potential to edit genes or block disease associated transcripts with nucleic acid therapeutics has tremendous potential for PD and AD. Mutations in the SNCA gene (which codes for α-synuclein) are linked to familial cases of PD, and expression of α-synuclein is a proven therapeutic target in sporadic PD (Rathnam, 2021). The APOE4 allele is the most important genetic risk factor in AD, and the silencing of the BACE1 gene (beta-secretase 1) leads to a decrease of amyloid-β production. But getting these nucleic acids into the brain has proven very challenging, because of their size, negative charge and low resistance to degradation by nucleases (Karthika et al., 2023).

The SARS-CoV-2 mRNA vaccines have proven to be a successful platform for delivering RNA, and lipid nanoparticles (LNPs) are emerging as the most prominent platform. A53T mice were treated intravenously with lipid nanoparticles encapsulating CRISPR-Cas9 mRNA and a single guide RNA targeting the SNCA gene (total of 2 mg/kg of nucleic acids, a week apart) (Sil et al., 2025). Surface functionalization with transferrin for BBB targeting and formulation with endosomal escape enhancing ionizable lipid SM-102. After four weeks of treatment, quantitative reverse transcription polymerase chain reaction (qRT-PCR) analysis of the substantia nigra revealed a 70% decrease in SNCA mRNA and immunohistochemistry and western blotting revealed a 65% decrease in α-synuclein protein (Katzengruber, Sander, & Laufer, 2023). These decreases in α-SYN were correlated with a 50% decrease in α-SYN aggregation and a corresponding improvement in motor performance in the rotarod test. Importantly, off-target editing at the top 10 predicted genomic sites was below the limit of detection, suggesting acceptable specificity. However, no evidence of an immune response against the Cas9 protein was seen, likely because of the relatively short expression window (less than 7 days) provided by mRNA delivery (Khan, Hu, Okeibunor, Ma, & Bopassa, 2025).

Lipid nanoparticles encapsulating BACE1-specific small interfering RNA (siRNA), were injected intravenously into the APP/PS1 mouse. siRNA is an approximately 21 bp double-stranded RNA that binds to the RNA-induced silencing complex and directs it to RNA targets that are complementary to siRNA and causes mRNA degradation. The rabies virus glycoprotein derived peptide RVG29 targeting the nicotinic acetylcholine receptor (nAChR) was used for functionalization of the lipid nanoparticles to improve BBB penetration. Following four weekly doses (2 milligrams siRNA/kg), BACE1 mRNA was decreased by 80% and BACE1 protein activity as measured by a fluorogenic substrate assay was decreased by 75% in the hippocampus (Khan et al., 2025). Amyloid-β level in the hippocampus was decreased by 70% and 65% for (1-40) and (1-42), respectively, and amyloid-β plaque burden was decreased by 60% by thioflavin-S staining. Reversal of cognitive deficits was observed in the treated mice in the Morris water maze and contextual fear conditioning tests. No liver enzyme elevations were detected nor were any other signs of toxicity. The siRNA effect was found to persist for about 3 weeks, after which the siRNA needed to be dosed repeatedly to maintain suppression (Kour, Dube, Kumar, & Panda, 2022).

In addition, exosomes have been loaded with siRNA. Table 2 summarizes the data from RVG29-modified exosomes loaded with siRNA against α-synuclein to remove α-synuclein aggregates in A53T mice.The results of the removal of α-synuclein aggregates in A53T mice by RVG29-modified exosomes loaded with siRNA against α-synuclein are summarized in Table 2. The exosome platform is low immunogenic, and does not require the use of synthetic lipids for delivery of the cargoes, but large-scale production is difficult.

Table 2: ***Comparison of neuroprotective nanoparticle platforms in PD/AD animal models.***

Nanoparticle Type	Cargo	Disease Model	Dose/Route	Efficacy Outcome	BBB Penetration
PLGA-PEG (Tf targeted)	GDNF	PD (6-OHDA rat)	2 mg/kg, IV	70% TH+ neuron preservation	Yes (RMT)
Cerium oxide (PEGylated)	None	AD (APP/PS1 mouse)	5 mg/kg, IP	50% reduction in Aβ plaques	Yes (adsorptive)
Lipid NP	CRISPR-SNCA	PD (A53T mouse)	1 mg/kg, IV	40% reduction α-syn mRNA	Yes (LNP)
Chitosan (lactoferrin)	BDNF	AD (rat)	200 µg, IN	Improved Morris water maze	Yes (intranasal)
Exosome (RVG)	siRNA-α-syn	PD (mouse)	100 µg, IV	60% reduction in α-syn aggregates	Yes (RMT)

4. Nanoparticle-Based Modulation of Neuronal Activity

4.1 Photothermal Modulation Using Gold Nanoparticles

In addition to bringing these neuroprotective molecules, nanoparticles can also be used to directly control the activity of neurons by transforming external light into local heat. This method involves the use of the strong surface plasmon resonance of gold nanoparticles which absorb energy from near-infrared light (usually 700-1100 Nm) and convert the light energy into heat with a photothermal conversion efficiency of more than 70%. The localized gold nanoparticles produce the rapid temperature increase (about 5-10 degree C above normal temperature) which can activate ion channels in neurons such as transient receptor potential vanilloid 1 (TRPV1) channel. TRPV1 is a non-selective cation channel that gets activated at temperatures above 43 degrees C, thus permitting a flow of calcium and sodium into the neuron and thereby depolarizing it (Krsek & Baticic, 2024). Importantly, unlike optogenetics, where the target cells have to be genetically modified, there are many populations of neurons in which TRPV1 is endogenously expressed (Rathore & Panwar, 2025).

Using a proof-of-concept study in PD models, the authors stereotaxically injected gold nanorods (GNRs) with an aspect ratio of about 4, having a longitudinal plasmon peak of 808 nm, into the subthalamic nucleus (STN) of mice, which is the

target for deep brain stimulation (DBS) in advanced PD. One week was allowed for accumulation before the near-infrared laser light (808 nm, 1 watts/cm2, 5 minutes) was passed through a fiber optic cannula. A thermocouple probe near the injection site recorded an increase in local temperature of 7 deg C. Firing rates of subthalamic nucleus neurons recorded in vivo electrophysiology were increased by this photothermal stimulation, and behavioral analysis showed that photothermal stimulation was able to suppress the amphetamine challenge-induced rotations by 80% in 6-OHDA-lesioned mice, similar to the effect of the conventional deep brain stimulation. Importantly, no evidence of tissue damage or protein denaturation was found with the laser parameters used as evaluated by hematoxylin and eosin as well as fluoro-jade staining of degenerating neurons. Subsequent studies by the same group showed that gold nanorods can be injected into the substantia nigra, from where they can be transported retrogradely to the subthalamic nucleus without any direct injection into the latter.

Photothermal modulation has been used to improve memory and synaptic plasticity in the hippocampus of AD animals (A. Kumar et al., 2023).

Gold nanospheres (50 nanometers diameter) were injected into the CA1 region of the Hippocampus of APP/PS1 mice that have been conjugated with an antibody against the neuron-specific cell adhesion molecule NCAM. Daily 2-week stimulation with near-infrared light (808 nm, 0.5 W/cm^2, 10 minutes) led to an increase in miniature excitatory postsynaptic currents of CA1 pyramidal cells, suggesting augmented synaptic transmission. The treated mice also performed better than untreated APP/PS1 mice on the novel object recognition task, with a discrimination index of 0.6, comparable to wild-type mice. The effect was persistent for 2 or more weeks after the last stimulation, indicating long-term potentiation-like changes in the strength of the synapses (M. Kumar et al., 2021).

One of the great strengths of photothermal modulation is its spatial specificity – the light can be focused to a spot size of less than one millimeter, so that a desired brain nucleus is stimulated while neighboring regions remain unaffected. The drawback is that near-infrared light still scatters in brain tissue, but is still useful for mouse and rat brain (about 2-3 cm in depth), and possibly useful for larger brains. However, there is a way to bypass this dilemma with implanted fiber optic cannulas and this is significantly less invasive than traditional DBS, which involves the implanting of metal electrodes and risks of infection and electrode fracture (Lakshmi Priya & Devi, 2025).

4.2 Magnetothermal Modulation Using Magnetic Nanoparticles

This is based on the concept that cells are affected by magnetic fields.This is based on the concept that cells react to magnetic fields.

To overcome the limitation of penetration depth of the photothermal approaches, magnetothermal modulation employs alternating magnetic fields that penetrate biological tissue without losing much strength. Superparamagnetic iron oxide nanoparticles (SPIONs) are usually 10-20 nm in diameter, and bring about heating when subjected to an alternating magnetic field due to Néel relaxation (rotation of the magnetic moment inside the particle) and Brownian relaxation (physical rotation of the particle). Specific absorption rate, which indicates the efficiency of heating, varies with the size, composition, coating and field parameters (amplitude and frequency) of the nanoparticles. If the product of amplitude and frequency exceeds 5 x 10^9 A·m-1·s-1, peripheral nerve stimulation and tissue heating would result, which is undesirable for biomedical applications (Lawal et al., 2022).

When attached to the TRPV1 channel, SPIONs can stimulate neurons in deep brain areas in milliseconds. Mice that express TRPV1 under the control of the tyrosine hydroxylase promoter were used in a landmark study that applied magnetothermal stimulation to the ventral tegmental area, which plays a role in reward processing. The SPIONs (10 nanometers coated with amino-silane for their conjugation to an antibody directed against TRPV1) were injected into the VTA and exposed to an alternating

magnetic field of 500 kHz, 15 kA/m, 5 minutes, via a copper coil above the animal's head (Leathem, Ortiz-Cerda, Dennis, & Witting, 2022). Local temperature rose by 6°C and in vivo fiber photometry recordings with the calcium indicator GCaMP6 revealed a rapid increase in activity of dopamine neurons, followed by a return to baseline temperatures within 10 seconds after the conclusion of the field. Magnetothermal stimulation was associated with place preference in the ventral tegmental area (VTA), as observed in behavioral analysis, suggesting the stimulation was rewarding (Liu, Li, Xie, Pan, & Shi, 2025).

In the case of PD, the stimulation of the subthalamic nucleus has been explored in 6-OHDA-lesioned rats. Anti-Kv4.3 antibody coupled SPIONs were injected to the subthalamic nucleus, which also has a temperature sensitivity (Lofts, Abu-Hijleh, Rigg, Mishra, & Hoare, 2022). Once-daily amphetamine-induced rotations were 75% less after 500 kilohertz, 20 kiloamperes/meter, 10-minute alternating magnetic field stimulation for one week, and these effects lasted for 48 hours following the last stimulation. Electrophysiological recordings showed subthalamic nucleus (STN) neurons were firing at higher rates when stimulated. Importantly, the same magnetic field parameters did not affect the sham-injected animals or animals injected with SPIONs without the targeting antibody, thus verifying the specificity (Lomboni, 2024).

In AD, magnetothermal stimulation has been used to promote LTP and memory in the hippocampus. Anti-TRPV1 antibody-SPIONs were injected into APP/PS1 mice in the CA1 region. Field excitatory postsynaptic potentials recorded from slices of hippocampal tissue were significantly larger following 2 weeks of daily alternating magnetic field stimulation (15 kiloamperes per meter 500 kilohertz for 10 minutes per day).After two weeks of field stimulations, the amplitude of field excitatory postsynaptic potentials (500 kilohertz, 15 kiloamperes per meter, 10 minutes per day) was significantly larger in slices of hippocampal tissue, reflecting improved synaptic plasticity (Lomboni, 2024). Mice treated with the drug had 25 seconds to escape the maze on Morris water maze while mice which were not treated took 60 seconds (wild-type 20 seconds). Furthermore, the c-Fos expression, a marker of neuronal activation, was enhanced in CA1 neurons of treated mice (Ravindranath & Grewall, 2024).

The main benefit of magnetothermal modulation over the photothermal technique is the ability to heat nanoparticles without the use of fibers anywhere in the brain. The alternating magnetic field can be produced with a coil placed outside of the animal's head and the field is uniform throughout the brain. The resolution, however, is not as good as light because the magnetic field cannot be focused as tightly; the stimulated region is about the diameter of the coil (1-2 cm in small animals). This is okay for stimulating nuclei like the subthalamic nucleus (STN) or the hippocampus, but not enough for more specific targeting. Further, the heat emitted by SPIONs fades with time, and repeated stimulation could ensue with cumulative heating effects. However, initial clinical trials of magnetothermal stimulation for brain tumors have shown that it is safe, and it is expected that within the next five years it will be translated to neurodegenerative diseases (Malviya, Singh, & Sharma, 2025).

Figure 3 shows nanoparticle mediated neuronal modulation in physical modes. Panel A shows photothermal modulation: gold nanoparticles (50 nanometers) attached to the TRPV1 channels on the membrane of a neuron; when the near-infrared light is on, it heats up the gold nanoparticles, causing the channels to open up, which leads to the influx of calcium and depolarization of the neuron. In the case of magnetothermal modulation, the superparamagnetic iron oxide (core diameter = 10nm) nanoparticles are driven by an alternating magnetic field (500 kHz, 15-20 kA/m) which produces heat by the Néel and Brownian relaxation mechanism, triggering temperature-sensitive TRPV1 or TRPM8 channels. Upconversion nanoparticle-enhanced optogenetics is represented in Panel C: Near-infrared light (980 nm) of the upconversion nanoparticles is converted to blue light (475 nm) that activates channelrhodopsin-2 expressed on

neurons, leading to the influx of cations and depolarization of the cells. Representative patch-clamp recordings of a neuron prior to, during, and after magnetothermal stimulation are shown in Panel D, showing that firing frequency of the action potentials increases during the stimulus.

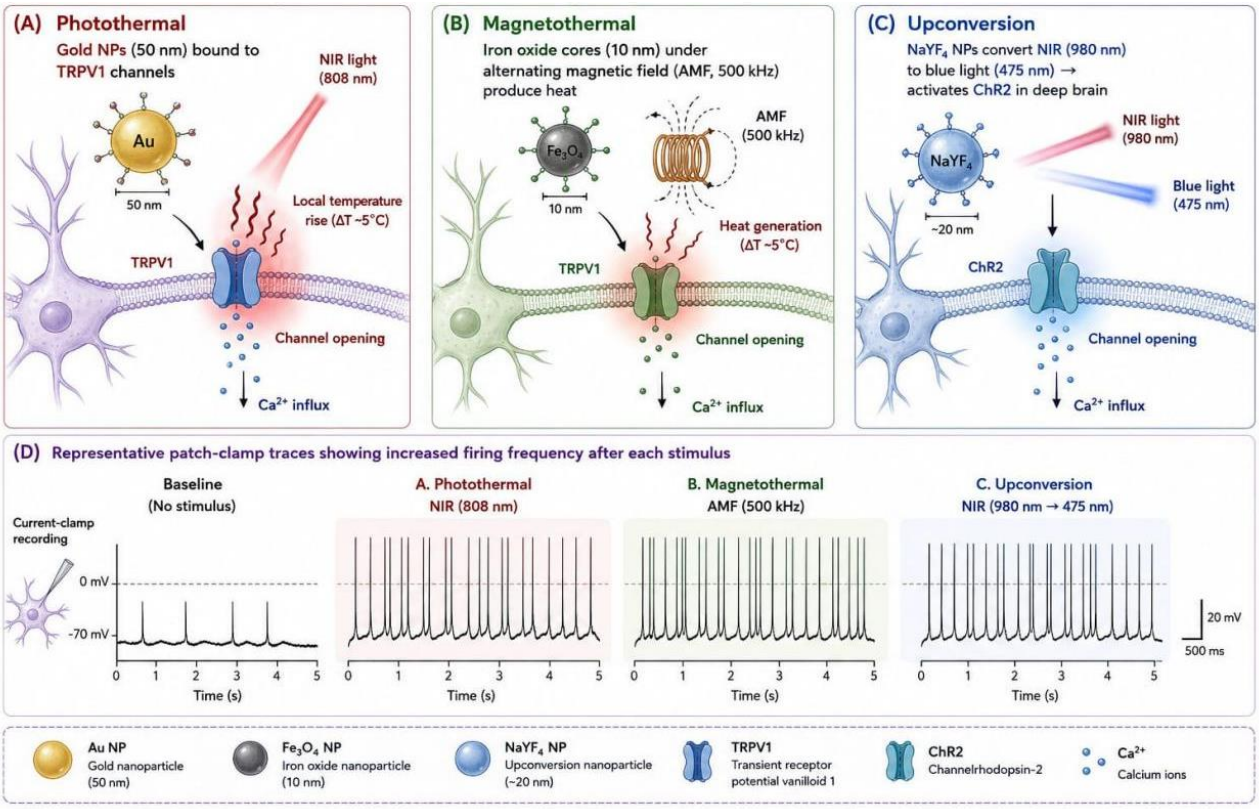


Figure 3: ***Nanoparticle-mediated physical modulation of neuronal activity***

4.3 Nanoparticle-Enhanced Optogenetics

The technique of optogenetics is very effective and involves genetically modifying neurons to express light-sensitive ion channels (such as channelrhodopsin-2) to control the neurons with light. The light used to activate channelrhodopsin-2, however, is blue (470 nanometers), which scatters strongly in brain tissue and only penetrates about 1 millimeter. Deeper areas like the substantia nigra or the hippocampus, on the other hand, demand invasive fiber optic implantations (Mani, Jindal, & Singh, 2023). This is overcome by the near-infrared UC nanoparticles, which convert the near-infrared light to visible light in the vicinity of the nanoparticles. The UCNPs are usually made of a crystal lattice composed of sodium ions and yttrium fluoride ions, with lanthanide ions like ytterbium (Yb^{3+}) used as a sensitizer, and thulium (Tm^{3+}) or erbium (Er^{3+}) used as an emitter. Near-infrared light (980 nanometers) is absorbed by Yb^{3+} and the energy used is passed to Tm^{3+}, causing it to emit blue light (475 nanometers) in a multiphoton upconversion process (Marcello & Chiono, 2023).

For the study that combined UCNPs with optogenetics, the A53T mice had channelrhodopsin-2 in their dopaminergic neurons, under the control of the tyrosine hydroxylase promoter, and were injected with UCNPs (40nm, coated with polyacrylic acid) into the substantia nigra. Near-infrared light (980 nanometers and 1 watt per cm2) was administered across the skull without a fiber implanted (Singh, Khan, & Song, 2025). A photomultiplier tube with a blue sensitivity was used for photometry recording and confirmed that the blue light

intensity produced by UCNPs was sufficiently high to activate channelrhodopsin-2. Near-infrared stimulation increased the firing rate of dopaminergic neurons from 2 hz to 15 hz in vivo, and behavioral analysis indicated that the stimulation reversed motor deficits in the rotarod test: The latency to fall increased from 30 seconds in unstimulated A53T mice to 120 seconds in stimulated mice, compared with 150 seconds in wild-type mice. Importantly, no off-target activation of non-channelrhodopsin-2 expressing neurons was observed as the blue light produced by the UCNPs was limited to the immediate vicinity (on the order of 50 micrometers) of the nanoparticles (Martinez & Peplow, 2022b).

A more recent development is the creation of UCNPs that are multi-coloured, that enable simultaneous activation of excitatory (channelrhodopsin-2, blue) and inhibitory (halorhodopsin, yellow) opsins. These allow for controlling the activity of neurons in both directions with one near-IR source (Soundara Pandi, Winter, Smith, Harkin, & Bojdo, 2025). Bidirectional control of channelrhodopsin-2 and halorhodopsin in an AD mouse model was demonstrated, with the activation of both channelrhodopsin-2 and halorhodopsin enhancing and decreasing epileptiform activity, respectively, and in turn improving memory and enhancing synaptic plasticity. A major hurdle towards clinical translation of UCNP-mediated optogenetics is the need to genetically modify human neurons to express opsins, which is impractical for most clinical trials. It is worth noting, however, that the approach could be useful in basic neuroscience studies and is potentially applicable in the future if viral vectors safe and efficient for human delivery of opsins are developed (Martinez & Peplow, 2022a).

4.4 Ultrasound-Sensitive Nanoparticles (Nanodroplets)

Mechanosensitive ion channels (e.g., Piezo1, TRAAK) are present on neurons and can be stimulated by mechanical forces such as ultrasound. To provide greater mechanical power to the focused ultrasound, perfluorocarbon nanodroplets (200-500 nanometers) have been created, which change from liquid to gas when they are pulsed by ultrasound of the appropriate strength. As the gas bubbles swell, they impose strong mechanical forces on neighbouring cell membranes which open mechanosensitive channels, and depolarize neurons without any genetic modification or heating of nanoparticles (Martos, Lőrinczi, Szatmári, Vécsei, & Tanaka, 2025).

The phase-change nanodroplets were made of perfluoropentane, which is a fat-soluble substance, and lipid, and injected into the rats' bloodstream. Focused ultrasound (1 megahertz, 1 megapascal, peak negative pressure) was then applied to a region of the motor cortex. The nanodroplets were transformed to microbubbles in the ultrasound field, and the mechanical deformation of neuronal membranes caused Piezo1 channels to be activated, as shown by the prevention of the effect by Piezo1 inhibitor, GsMTx4. The electrophysiological recordings demonstrated that the firing rate of motor cortex neurons was enhanced from 1 Hz to 20 Hz when the nanodroplet cavitation was induced by ultrasound, and the behavioral analysis demonstrated that the movements of contralateral forelimb were time-locked to the ultrasound pulses (Martos et al., 2025). In a PD rat model, the use of ultrasound-sensitive nanodroplets targeted to the subthalamic nucleus resulted in 70% fewer amphetamine-induced rotations, similar to what was observed with deep brain stimulation. No tissue damage or haemorrhage was seen on post mortem histology, and effect reversed in just a few minutes after stopping the ultrasound exposure (Mehanna et al., 2025).

The benefits of this include no genetic modification, no need to inject nanoparticles into the brain and the spatial precision of focused ultrasound (millimeter scale). However, some limitations are that the specialized ultrasound equipment is required and the temporal resolution is relatively low, at the millisecond scale, compared to the temporal scale of optogenetics (microsecond scale). However, ultrasound-sensitive nanodroplets are among the most clinically translatable neuromodulation strategies as focused ultrasound is FDA approved

for essential tremor and is being explored for several brain disorders (Mohammadkhanizadeh et al.).

5. Theranostic Nanoparticles Combining Imaging and Therapy

5.1 MRI-Guided Therapy

Superparamagnetic iron oxide nanoparticles are powerful T2 magnetic resonance imaging (MRI) agents due to the high magnitude of the magnetic field inhomogeneities they generate, which result in shortening of T2 relaxation times and thus dark areas on T2-weighted images. Intravenous administration of the transferrin-conjugated SPIONs loaded with GDNF was carried out in the 6-OHDA-lesioned rat and T2-weighted MRI at 7 Tesla showed a dark MRI signal in the SN and the ST that reached the maximum at 24 hours and remained present for 7 days (Mohammadkhanizadeh et al.). The MRI signal intensity was quantitatively correlated with the measured iron concentration by inductively coupled plasma mass spectrometry (ICP-MS) (R2 = 0.92) and with measurement of GDNF levels by enzyme-linked immunosorbent assay (ELISA) (R2 = 0.85) to enable the non-invasive estimation of drug delivery. The same nanoparticles were therapeutic and maintained 70% of tyrosine hydroxylase-positive neurons. This proves that MRI can be used to identify patients with optimal delivery of nanoparticles and to optimise the dose delivered (Munteanu, Galaction, Onose, Turnea, & Rotariu, 2025).

5.2 Fluorescence and Photoacoustic Imaging

Near-infrared imaging using carbon dots, fluorescent nanoparticles smaller than 10 nanometers has been used to image amyloid-β plaques. APP/PS1 mice were injected intravenously with curcumin loaded carbon dots (700 nm) and live in vivo two-photon imaging of the mouse brain was performed through the entire skull, where structures labeled as plaques were identified that colocalized with thioflavin-S staining on post-mortem brain sections (Nasibova, Alyarbayova, & Maharramova, 2025). Plaque burden was significantly correlated with fluorescence signal intensity (R^2 = 0.78) and enabled longitudinal assessment of the disease and treatment outcomes in the same animal. As opposed to fluorescence imaging, which has a limited penetration depth (up to 1 centimeter), photoacoustic imaging detects ultrasound waves produced by the rapid heating of nanoparticles after pulsed laser excitation, resulting in greater depth of penetration (up to 5 centimeters). The mice were successfully imaged with gold nanorods with a peak absorption of 808 nanometers, and the amount of 10 picomolar of the nanorods was enough to image the substantia nigra. In parallel, the same gold nanorods were employed in the photothermal modulation to establish a complete theranostic platform (Nag et al., 2024).

5.3 PET/SPECT-Active Nanoparticles

Radiolabeled nanoparticles are critical to quantitative biodistribution studies and to human translation of single-photon emission computed tomography (SPECT) or positron emission tomography (PET) studies because they allow for absolute quantification of concentration of the nanoparticles, and also do not permit depth-dependent signal attenuation. A DOTA chelator has been used to chelate copper-64 (with a half-life of 12.7 hours) to PLGA nanoparticles. In vivo imaging of ^{64}Cu-PLGA-Tf in rats revealed that the nanoparticles targeted to transferrin progressively increased in the brain over a 24-hour period, peaking at 0.8 percent injected dose per gram in the striatum. Brain uptake was totally inhibited by excess free transferrin, establishing the existence of receptor-mediated transcytosis (Naz & Siddique, 2021). Adoptive transfer of the same nanoparticles containing curcumin to APP/PS1 mice resulted in a decrease in amyloid-β plaques, thus proving that the radiolabeling does not affect the therapeutic activity of the nanoparticles. For longer term monitoring of nanoparticles in non-human primates, zirconium-89 (half-life 78.4 h) has been employed, and uptake in the brain of non-human primates has been observed up to 5 days post injection (Nunes, Loureiro, & Pereira, 2022).

Table 3 shows the representative theranostic nanoparticles used in PD and AD, along with the imaging modality, composition of nanoparticles, therapeutic cargo, disease model, and the key

findings. In PD rats, MRI-guided transferrin-SPIONs containing GDNF allowed for the correlation of MRI signal with dopamine recovery. Longitudinal monitoring of plaque reduction was accomplished using near-infrared fluorescent carbon dots containing curcumin in AD mice. In PD mice, photoacoustic imaging of gold nanorods (no cargo) enabled the imaging during photothermal stimulation. Brain uptake (0.8% ID per g brain) of 64Cu-PLGA- Curcumin nanoparticles has been quantified by PET in AD rats. These theranostic platforms will help bring image-guided, personalized nanomedicine to the treatment of neurodegenerative diseases (Okafor, Omoteso, & Nnaji, 2025).

Table 3: ***Summary of theranostic nanoparticles for PD/AD.***

Imaging Modality	Nanoparticle	Therapeutic Cargo	Disease Model	Key Finding
MRI	SPION (Tf-targeted)	GDNF	PD (rat)	NP localization correlated with dopamine recovery
NIR fluorescence	Carbon dots	Curcumin	AD (mouse)	Reduced Aβ plaques and NIR imaging of plaque burden
Photoacoustic	Gold nanorods	None (photothermal)	PD (mouse)	Real-time imaging of NIR stimulation

6. In Vivo Evidence from PD and AD Animal Models

6.1 Rodent Models of Parkinson's Disease

Unilateral injection of 6-hydroxydopamine (6-OHDA), which selectively and irreversibly destroys dopaminergic neurons, is the 6-hydroxydopamine model. This model has been generally adopted due to the ability to obtain a quantifiable behavioral asymmetry (amphetamine-induced rotation) that can be used as a measure of nigrostriatal integrity (Polshettiwar, Khuspe, Gholap, Aldar, & Godbole, 2025). The most consistent findings from studies on the neuroprotective efficacy of nanoparticles containing GDNF, curcumin, or minocycline are that 70–90% of lesions treated with these nanoparticles compared to untreated lesions result in the reduction of rotations, which equates to 60–80% preservation of tyrosine hydroxylase-positive neurons. Behavioral recovery follows the time course of sustained release of the nanoparticles (2-4 weeks) and repeated doses prolong the effect (Ore, Angelastro, & Giulivi, 2024).

In the MPTP model, MPTP is systemically injected; it is metabolized to the toxic compound MPP^+, which crosses the Dopamine Transporter into dopaminergic neurons and binds to and inhibits mitochondrial Complex I, leading to acute cell death. This model mimics oxidative stress and neuroinflammation in human PD. Of note, intravenous and intraperitoneal injections of CeO2NPs have consistently resulted in neuroprotection in the MPTP model, where tyrosine hydroxylase-positive neurons and striatal dopamine levels were preserved, while microglial activation and release of pro-inflammatory cytokines were reduced. Typical effect size is about 50-80% of the preserved animals, vs about 30% of the non-treated mice. Additive or synergistic effects have been observed with combination therapy, such as cerium oxide and minocycline-loaded nanoparticles (Storka et al., 2015).

A53T transgenic mouse is a spontaneous model in which human mutant α-synuclein is expressed in an increasing amount driven by the prion promoter, resulting in progressive accumulation of α-synuclein aggregates, motor deficits beginning at 6-9 months of age and diminished lifespan. This model is more pathophysiologically relevant than toxin models since the same protein that aggregates in humans with PD is used (Ouerdane et al., 2022). In the A53T mice, the α-synuclein aggregates were decreased by 60-70% and the lifespan was increased by about 20% after the use of curcumin PLGA nanoparticles. The gene targeting with the CRISPR lipid nanoparticles resulted in a 65–70% decrease in α-synuclein mRNA and protein and an improvement in motor performance in the rotarod and pole tests. Most importantly, efficacy in the A53T model is seen as more predictive for human response than efficacy in toxin models (Roy, Paul, Bhattacharya, & Borah, 2023).

A) Tablet 2: Rodent Models of Alzheimer's Disease.A) Tablet 2: Rodent Models of Alzheimer's Disease.

APP/PS1 double transgenic mice express human APP by the Swedish mutation (KM670/671NL) and PS1 by the L166P mutation from the prion promoter, and develop amyloid-β plaques from 4-6 months and cognitive dysfunction from 8-12 months of age. According to this model, anti-aggregation nanoparticles (curcumin-PLGA, gold nanoparticles) successfully decrease the level of amyloid-β (Aβ) plaques by 50-70% by immunohistochemistry, thioflavin-S staining and enzyme-linked immunosorbent assay. The decrease in plaques is accompanied with increased performance in the Morris water maze (decreased escape latency time, increased time in target quadrant), novel object recognition (increased discrimination index), and contextual fear conditioning (increased freezing). Cognitive improvement is correlated with the amount of plaque reduction (R^2 ~ 0.6-0.7) but in some cases a significant amount of cognitive improvement occurs without significant plaque reduction, suggesting other mechanisms like reduced oligomer toxicity or improved synaptic function (Suchiita, Gupta, Nandi, & Goswami, 2025).

The 5xFAD mouse is an expression of 5 familial AD mutations and exhibits a more aggressive phenotype with plaques present at 1.5-2 months and cognitive deficits at 4 months. This model has been employed to evaluate the effect of neuroprotective nanoparticles which also inhibit neuroinflammation or/or oxidative stress. Minocycline loaded in the lipid nanoparticles and resveratrol loaded in the chitosan nanoparticles reduced the activation of microglia and preserved the synaptic proteins (synaptophysin, PSD95) in 5xFAD mice, and improved the cognitive function despite the fact that only 20–30% of the plaque reduction was observed. This indicates that the anti-inflammatory and anti-oxidative treatments could be as crucial as amyloid-β treatment itself.

In vivo effectiveness of APP/PS1 mouse model of Alzheimer's disease when treated with transferrin-targeted curcumin-PLGA nanoparticles is shown in figure 5. Experimental timeline in panel A: 8-month-old mice were intravenously injected with nanoparticles (2mg/kg of curcumin) twice a week for four weeks before performing behavioral tests and histology. Panel B: Morris water maze results: mice treated with nanoparticles (filled circles) had significantly reduced escape latency when compared with untreated APP/PS1 mice (open triangles) starting from day 3 of training ($p<0.01$), and similar to wild-type controls (open squares). Panel C depicts staining with thioflavin-S in hippocampal sections: untreated APP/PS1 mice have many bright green plaques whereas nanoparticle-stained mice have a significant reduction in plaques, with a quantitative reduction in plaque area of 65%, $p<0.001$. Enzyme-linked immunosorbent assay (ELISA) analysis of IL-1β (panel D) and tumor necrosis factor (TNF) (panel D) levels in the homogenates of the hippocampus indicated that both cytokines were significantly increased in the untreated APP/PS1 mice and significantly decreased in the homogenates from the nanoparticle-treated mice ($p<0.01$ and $p<0.01$, respectively). Panel E demonstrates the immunostaining of NeuN (neuronal nuclei) in the CA1 region: APP/PS1 mice without nanoparticles have a reduced number of neurons (about 40% less), while those

treated with the nanoparticles have a normal number of neurons.

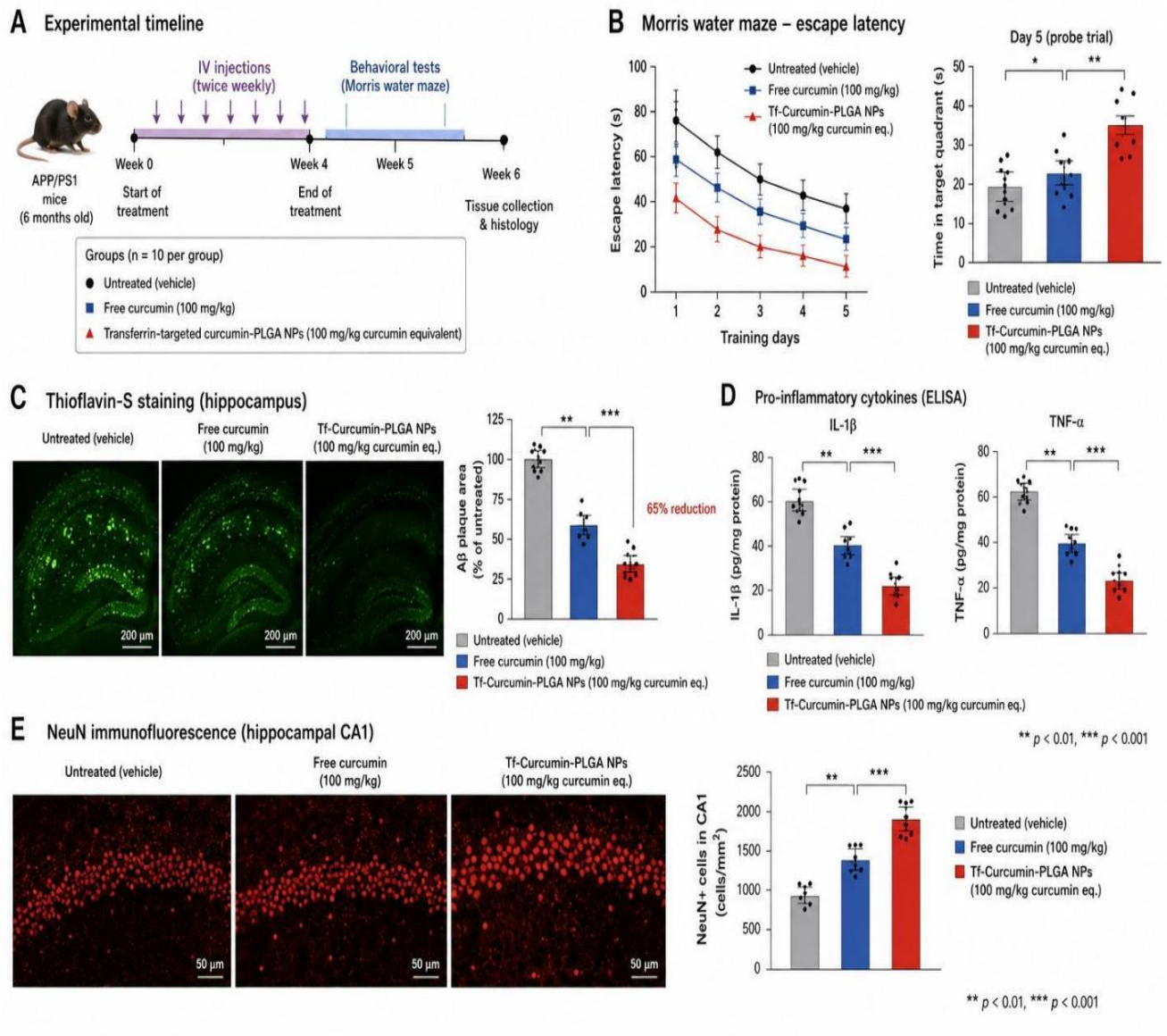


Figure 4: ***In vivo therapeutic efficacy of transferrin-targeted curcumin-PLGA nanoparticles in APP/PS1 Alzheimer's disease mouse model.***

6.3 Large Animal and Non-Human Primate Studies

Rodent studies are useful for initial proof-of-concept; however, non-human primate studies are important for translation due to the primate brain being larger, with lower permeability BBB, and complex cognitive and motor behavior. Transferrin-targeted PLGA nanoparticles loaded with GDNF were only tested in one study in MPTP-treated cynomolgus monkeys. The six weekly doses of nanoparticles (1mg of GDNF equivalent/kg of monkey). The group that received the GDNF nanoparticles had a parkinsonism rating scale (a clinical measure of tremor, bradykinesia (slow movement) and posture) of 12 at the beginning of the study, which

dropped to 6 after 6 weeks – a significant improvement, whereas the controls (those that received free GDNF or empty nanoparticles) did not improve. Only the monkeys treated with nanoparticles had increased dopamine synthesis capacity in the putamen as measured by PET with 6-^{18}F-fluoro-L-DOPA (20% increase from baseline) (Supriya et al., 2025).

A stereological post-mortem analysis of substantia nigra tissue showed 55% preservation of tyrosine hydroxylase positive neurons. No dyskinesia or loss of weight was observed. This study shows compelling evidence for achieving disease-modifying effects with systemic delivery of nanoparticles in a species that holds high translational relevance to humans. But, larger primate studies with longer duration of follow-up (12 months or greater) are required to evaluate durability and safety (A. Tiwari et al., 2025).

7. Safety, Toxicity, and Biodegradation of Nanoparticles

7.1 Acute and Chronic Toxicity

Nanoparticles are safe depending on the composition, size, surface charge and route of administration (Ovejero, Wang, Veintemillas-Verdaguer, Morales, & Sorolla, 2021). The main organs in which nanoparticles can accumulate for systemic administration are the liver and spleen because Kupffer cells and splenic macrophages have phagocytic properties. Acute toxicity testing in mice and rats indicates a median lethal dose (LD50) of more than 500–1000 milligrams per kilogram for a majority of biodegradable nanoparticles (PLGA, chitosan, lipid nanoparticles), significantly higher than the therapeutic dose (usually 1–10 milligrams per kilogram). Repeated dosing studies (100 mg/kg, once a month for 6 months) in rodents have not demonstrated any hepatotoxicity or nephrotoxicity based on the blood levels of the serum enzymes alanine aminotransferase, aspartate aminotransferase, creatinine, and blood urea nitrogen, however the LD50s of non-biodegradable nanoparticles (e.g., gold and cerium oxide) are 100-200 mg/kg, and they have been found to accumulate in the liver and spleen for months. Reversible for biodegradable formulations, some macrophage vacuolization and mild fibrosis are observed at high dose (above 50 mg/kg) on histological examination of liver and spleen (N. Patel et al., 2025).

Another problem area with brain penetrant nanoparticles is unintended deposition in the brain parenchyma outside the target area. Receptor-targeted nanoparticles are found to have the greatest accumulation in the targeted brain area (substantia nigra or hippocampus) as well as other brain areas with lower receptor expression and, interestingly, the choroid plexus and circumventricular organs which lack a tight BBB (Tiwari, Dwivedi, Kaushik, Tripathi, & Dada, 2025). With repeated doses, there could be some buildup of nanoparticles in non-target areas of the brain. However, long-term studies (6 months of weekly administration) of PLGA nanoparticles have failed to show any signs of degeneration, gliosis, or behavioral abnormalities other than the therapeutic effects (Patel, Thornton, & Parmar, 2025).

7.2 Neuroinflammation from Nanoparticles

Believe it or not, some nanoparticles, especially those that have a positive zeta potential (zeta potential > +20 millivolts) or non-biodegradable cores (gold, silica) can trigger the activation of microglia and the induction of neuro-inflammation. The uptake of cationic nanoparticles by microglia through scavenger receptors and their ability to activate the NLRP3 inflammasome causes the release of IL-1β and neurotoxicity. Therefore, most of the formulations containing nanoparticles for brain delivery are modified with polyethylene glycol (PEG) or neutral polysaccharide (Dextran) to decrease the surface charge and decrease microglial recognition. Microglia uptake of PEGylated nanoparticles is decreased by ~80% when compared with non-PEGylated nanoparticles, as determined by flow cytometry of primary microglia. When not PEGylated, biodegradable nanoparticles (PLGA and chitosan) do not generate significant microglial activation because they are slowly degraded into lactic acid and glycolic acid or glucosamine, which are metabolized by normal cellular pathways (Pokrzyk,

Kulczyńska-Przybik, Guzik-Makaruk, Winkel, & Mroczko, 2025).

Quantification of inflammatory responses to nanoparticles can be obtained by measuring level of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) in brain homogenates or immunohistochemistry of microglial (Iba-1, CD68) and astrocytic (GFAP) markers. If optimized formulations (PEGylated PLGA, transferrin-targeted, dose < 10 milligrams per kilogram) are used, the levels of cytokines are not significantly different from saline-injected controls and immunoreactivity for Iba-1 exhibits resting microglial morphology with small cell bodies and fine processes, but not activated microglial morphology with enlarged cell bodies and retracted processes (Polshettiwar et al., 2025).

7.3 Protein Corona Effects

Once in the bloodstream, the protein corona forms around the nanoparticles. The composition of the corona, which is comprised of serum proteins such as albumin, apolipoproteins, complement proteins and immunoglobulins, varies with size, surface chemistry and serum source of the nanoparticles (Polshettiwar et al., 2025). The protein corona may affect the behavior of nanoparticles in a number of ways: it could mask targeting ligands, thereby decreasing the amount of receptor mediated transcytosis; it could cause macrophages to uptake the nanoparticles from the reticuloendothelial system and decrease the delivery of the nanoparticles to the brain; and it could activate immune responses, such as complement activation or antibody production. For instance, transferrin-conjugated nanoparticles bind to transferrin that forms a protein corona that partially interferes with transferrin binding resulting in a reduction of BBB transcytosis of around 50% in vitro (Turkez et al., 2025).

Possible methods that can be used to reduce the protein corona include dense PEGylation, using high molecular weight PEG (5–10 kilodaltons) with high grafting density, and zwitterionic coating (e.g., carboxybetaine) and pre-coating with the "stealth" protein CD47. The field is actively trying to develop nanoparticles that do not adsorb proteins, but it may not be possible to completely inhibit the formation of protein corona around the nanoparticles, so the corona should perhaps be viewed as an integral part of the nanoparticles' biological identity instead of an artifact (Prajapati et al., 2025).

7.4 Regulatory Considerations

The regulations for nanotechnology-based drugs to treat neurodegenerative diseases are complicated because these products are generally classed as combination products (drug + device or biologic + device). Most nanoparticle drug formulations are regulated by the FDA's Center for Drug Evaluation and Research (CDER) and those containing nucleic acids or viral vectors by the Center for Biologics Evaluation and Research (CBER). The Center for Devices and Radiological Health (CDRH) is also involved for nanoparticles that contain a diagnostic imaging agent. For 1st-in-human trials, there are two required species of GLP toxicology studies (generally rodent and non-rodent, such as rat and dog, or NHP) and a dosing duration of at least the same duration as the proposed clinical trial. The studies should include acute toxicity (single dose, 14 day observation), subchronic toxicity (repeat dosing for 28-90 days), genotoxicity (Ames test, micronucleus assay), and for nanoparticles that bioaccumulate in brain, neurobehavioral and neuropathology assessments (Prajapati et al., 2025). There are no nanoparticle-based therapeutics approved for PD or AD to date, although a number of these therapeutics have finished Phase I or II trials with other CNS indications.Currently, no PD/AD-approved nanoparticle-based therapeutics exist, but a number of these therapeutics have completed Phase I or II trials in other CNS indications (Prasanth, Mallya, Cho, & Mundekkad, 2025).

Toxicity profile of commonly used nanoparticles that have been proposed for neuroapplications is summarized in Table 4. PLGA (weeks biodegradable) has no BBB disruption, low microglial activation, and LD50 > 500mg/kg in mice. PEGylated gold nanoparticles (5–20 nm, non-biodegradable) show BBBD and low microglial activation, and have a LD50 greater than 100 mg/kg.PEGylated cerium oxide (non-biodegradable) shows no BBB disruption, low

microglial activation with PEG, and LD50>200 mg/kg. These data suggest PEGylated, biodegradable nanoparticles are the most clinically appropriate with regard to their safety (Verma, Pathak, Shukla, & Sonar).

Table 4: ***Toxicity profile of commonly used nanoparticles in neuroapplications.***

Nanoparticle Material	Biodegradable	BBB Disruption	Microglial Activation (in vivo)	LD50 (mouse, IV)
PLGA	Yes (weeks)	No	Low	>500 mg/kg
Cerium oxide	No	No	Low (PEGylated)	>200 mg/kg
Gold (5-20 nm)	No	No (with PEG)	Moderate (non-PEG)	>100 mg/kg
SPION (iron oxide)	Yes (months)	No	Low (dextran-coated)	>300 mg/kg
Chitosan	Yes (days)	No	Low	>1000 mg/kg

8. Clinical Translation Status

8.1 Completed and Ongoing Clinical Trials

None of the nanotherapies for Parkinson's or Alzheimer's reached the FDA or EMA approval in 2025, specifically. Several related nanomedicines have been taken out of the laboratory and into the clinic, however, and offer proof-of-concept for the field. Ferumoxytol, a nanotechnology iron oxide compound developed for the treatment of iron-deficiency anemia, is now being used as an MRI contrast agent to assess neuroinflammation in PD patients (Vietor et al., 2023). Ferumoxytol-enhanced MRI was used to detect the presence of iron in the substantia nigra of PD patients versus healthy controls, which showed an increase in iron in the patients, and the signal corresponded to the severity of the disease as measured by the Unified Parkinson's Disease Rating Scale in a Phase II trial (NCT02847130). These indicate that ferumoxytol may be a potential biomarker for PD progression and selection of suitable patients for therapeutic studies (Abdelmonem et al., 2024).

Nanoliposomal curcumin (NanoCurc) has passed the Phase I trial in healthy volunteers and the Phase I/II trial in mild to moderate AD patients (NCT03542670). The formulation is made up of curcumin loaded in PEGylated liposomes (PegLiposomes) of size 100nm. Single intravenous doses of up to 400mg CEA curcumin were well tolerated in the Phase I trial, without any dose limiting toxicities or serious adverse events. The plasma amyloid-β level reduction and improvement in cognitive scores on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) were observed at 12 weeks in the treatment group of 12 patients using nanoliposomal curcumin compared with the placebo group of 12 patients, but the changes were not statistically significant ($p = 0.09$). This was probably an underpowered trial and another such Phase II study is planned (Abdelmonem et al., 2024).

As with the COVID-19 vaccines, lipid nanoparticles (LNPs) developed for the delivery of mRNA have been introduced into Phase I trials for the delivery of neurotrophic factors. In 2023, a Phase I intrathecal LNP-encapsulated GDNF mRNA trial commenced in PD patients (NCT04167540) and is targeted to be completed in 2026. Best measured endpoints are safety and tolerability, secondary endpoints are cerebrospinal fluid GDNF levels and clinical rating scales. If

successful, this would be a significant step toward nanomedicine-based gene therapy against neurodegenerative diseases (Wei et al., 2024).

8.2 Key Challenges for Clinical Translation

Though promising preclinical results have been obtained, several issues need to be solved before the use of nanoparticle therapy in PD and AD can be clinically implemented. First scalability and Good Manufacturing Practice (GMP) production: nanoparticles obtained in the lab on a small scale (e.g., by thin-film hydration, double emulsion, nanoprecipitation) can be variable from batch to batch, and scaling up to kilogram quantities demands a careful optimization of the process. The production of research-grade nanoparticles is a 10- to 100-fold more expensive than the production of GMP-grade nanoparticles, and it demands a lot of quality control testing (size, polydispersity, surface charge, drug loading, release profile, sterility, endotoxin levels). Second, long-term safety data are not available, as most preclinical studies last only 1–6 months, and most patients with PD and AD would need to take medicines for years, or even decades. Large animal (12 months or more) chronic toxicity studies are needed to evaluate the risks of chronic accumulation of nanoparticles in the liver, spleen and brain. Third, it is not clear how best to give this treatment. IV is convenient, but does not result in significant brain accumulation (0.1–1% of injected dose) even when active targeting is used (Yagmurlu, Hamilton, Szidonya, Barajas, & Iv, 2024).

Intranasal bypasses first pass metabolism and is mainly delivered into the anterior brain and the olfactory bulb; there is also low distribution into the substantia nigra or hippocampus. Intrathecal or intracerebroventricular (ICV) injection results in high levels of the drug in the brain, but is invasive and has the potential for infection and catheter complications. Fourth, patient selection and the use of biomarkers is essential: since the BBB is not disrupted in early PD and AD, receptor-targeted nanoparticles can have to compete with endogenous ligands. Patients with more severe disease may have dysfunction of the BBB which can enhance the penetration of nanoparticles, but also may have more widespread neurodegeneration, which may be irreversible. Target engagement [PET, MRI] is required to verify engagement and inform dose selection (Sarker & Franks, 2018).

9. Future Directions and Unanswered Questions

9.1 Personalized Nanoparticles

Based on the genetic and molecular diversity of PD and AD, this is not the best strategy to achieve optimal results with a one-size-fits-all nanoparticle solution. Some examples include: SNCA mutation patients could receive α-synuclein lowering gene therapy, LRRK2 mutation patients could receive kinase inhibitors, and sporadic patients with dominant neuroinflammation could receive anti-inflammatory nanoparticles (Zala, Banerjee, & Tiwari, 2025). Use of patient specific antibodies or aptamers as targeting ligands would enable the design of personalised nanoparticles. One strategy is to screen the serum of each patient for autoantibodies specific for brain antigens (alpha-synuclein, amyloid-β), and then functionalize nanoparticles with these autoantibodies. This will do both active targeting and may offer therapeutic benefit because the autoantigen will be cleared. The purified PD patients' serum IgG, which contained anti-α-synuclein antibodies, were shown to bind better with α-synuclein aggregates in vitro, and decreased aggregate burden in A53T mice compared to nanoparticles coated with control IgG in a proof of concept study. However, personalized nanomedicine is still in its early stages and has tremendous potential (Zambonino et al., 2023).

9.2 Closed-Loop Nanosystems

Closed-loop or "smart" nanosystems deliver therapeutic agents in response to a particular biomarker, allowing for treatment when needed. In the case of PD, nanosensors which sense the level of dopamine in the brain could release levodopa once the level is below a threshold (Yadav et al., 2025). For instance, dopamine-imprinted polymer nanoparticles switch shape when dopamine binds to them, thus releasing encapsulated levodopa. When the dopamine level drops below 20% of normal, the released levodopa

replenished the dopamine level back to normal for about 4 hours before resetting. This way, the amount of dopamine released mimics the normal, pulsatile, and physiological release and avoids the high levels that would otherwise cause dyskinesia. Nanosensors for the detection of amyloid-β oligomers or hyperphosphorylated tau in AD could release anti-aggregation agents or anti-inflammatory drugs (Yuao Wu, Moonshi, & Ta, 2025).

9.3 Regulatory Pathways for First-in-Human Trials

For the first PD/AD therapy based on nanoparticles a clear regulatory roadmap is warranted. In the short run, LNPs carrying mRNA or siRNA are the most promising candidates as the LNP platform has been approved by the FDA for other indications and the safety profile is well established. A Phase I trial may include both early-stage patients with PD or AD (Hoehn and Yahr stage 1-2 for PD; Clinical Dementia Rating 0.5-1 for AD) and may involve administration of a single dose of LNP-encapsulated siRNA against either SNCA or BACE1 via intrathecal injection (Yu Wu & Angelova, 2023).

The safety would be the primary endpoint, including adverse events, cerebrospinal fluid cell counts, protein levels, MRI of inflammation or hemorrhage. Secondary endpoints would be target engagement (reduction in SNCA or BACE1 mRNA and protein exosomes in CSF) and exploratory biomarkers (CSF α-synuclein or amyloid-β levels). Once confirmed that it is safe and effective to engage the target, a Phase II trial involving a larger number of patients and multiple doses could be used to determine clinical efficacy. With the need for disease-modifying treatments in PD and AD, regulatory agencies have set up expedited pathways (Fast Track, Breakthrough Therapy, Regenerative Medicine Advanced Therapy) that may help expedite development (Zambonino et al., 2023).

10. Conclusion

Nanoparticle platforms are a revolutionary way to protect and modulate the brain in Parkinson's disease and Alzheimer's disease. In extensive preclinical studies, antioxidant nanoparticles (cerium oxide), anti-aggregation nanoparticles (curcumin-PLGA, gold), anti-inflammatory nanoparticles (minocycline lipid carriers, resveratrol chitosan), neurotrophic factor-loaded nanoparticles (GDNF-PLGA, BDNF chitosan), and gene therapy nanoparticles (CRISPR LNPs, siRNA exosomes) have been shown to improve neuroprotection, attenuate oxidative stress, protein aggregation, and neuroinflammation while maintaining neuronal survival and function in rodent and primate models. For neuromodulation, photothermal (gold nanoparticles), magnetothermal (SPIONs), optogenetic (upconversion nanoparticles) and ultrasound-sensitive (perfluorocarbon nanodroplets) platforms allow non-invasive or minimally invasive modulation of neuronal activity with spatial and temporal precision, to rescue motor and cognitive deficits without genetic modification.

The theranostic nanoparticles can incorporate multiple imaging modalities such as MRI, fluorescence, photoacoustic, or PET imaging and therapy, enabling real-time monitoring of the biodistribution and target engagement of nanoparticles. Biodegradable formulations (PLGA, chitosan, lipid nanoparticles) have favorable safety profiles in subchronic studies but lack long-term toxicity study data. Clinical translation is still early, the closest candidates are ferumoxytol (MRI) and nanoliposomal curcumin (Phase I/II) and are planned in the upcoming years. Personalized nanoparticle functionalization, closed-loop release systems that are triggered by disease biomarkers, single platforms that allow for the integration of neuroprotection and neuromodulation, machine learning based designs, and accelerated regulatory pathways are some of the key future directions that are envisioned. Although there are still great obstacles to overcome, within the next ten years, the synergy of nanotechnology, neuroscience and gene therapy is expected to provide the first disease-modifying treatments for Parkinson's and Alzheimer's disease.

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