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Targeted quantum dots: A novel approach for diagnosis and treatment of neurodegenerative diseases

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ABSTRACT

Nanotechnology-based approaches using quantum dots (QDs) are attracting growing attention for neurodegenerative diseases. These include carbon- and graphene-based nanostructures, ZnO QDs, and emerging black phosphorus nanomaterials, all of which serve as multifunctional theranostic platforms. QDs possess unique properties derived from their crystalline inorganic lattice structures, strong ionic/covalent bonding, optical features, and tunable surfaces. These attributes enhance their applicability in drug delivery, molecular imaging, and biosensors. Furthermore, the ability of QDs to cross the blood-brain barrier (BBB) via receptor-mediated, adsorptive, or carrier-assisted pathways has driven the development of advanced surface functionalization strategies to improve targeting specificity and biocompatibility. This review focuses on the application of targeted QDs in major neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS), highlighting recent preclinical advances, diagnostic and therapeutic mechanisms, and BBB transport strategies. Despite these advances, challenges such as long-term toxicity, biological stability, regulatory approval, and scalable synthesis must be addressed to realize the clinical potential of QD-based nanomedicine in neuroscience fully.

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Introduction

Neurodegenerative disorders are a major global health challenge that is multifactorial, primarily comprising genetic, environmental, and age-related factors. A hallmark of these diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, systemic amyloidosis, and a variety of progressive and frequently incurable diseases of the central nervous system (CNS)(1), is the excessive accumulation of misfolded proteins in either the extracellular or intracellular space (2). Therefore, the inflammatory response caused by the activity of glial cells, in particular, microglia and astrocytes, and the synthesis of pro-inflammatory cytokines and reactive oxygen species (ROS) is the result of disrupting cellular homeostasis by aggregation. Moreover, mitochondrial dysfunction is a key factor in chronic neuroinflammation due to its role in the induction of harmful neurodegenerative mechanisms (3). The common hurdles in treating neurodegenerative diseases predominantly include delivering drugs across the blood-brain barrier, the inability to make an early diagnosis, and the multifactorial pathogenesis of these diseases. The latest breakthroughs in nanotechnology, especially quantum dots (QDs), present some potential alternatives to traditional approaches to treatment and diagnosis of neurological diseases (4).

QDs, as new nanoplatforms in the neurodegenerative disease arena, exhibit greater surface reactivity and cellular internalization due to their unique properties. Notably, their small size enables them to cross the blood-brain barrier (BBB), a significant barrier to treating neurological diseases such as AD and PD (5). BBB transport mechanisms can be categorized into three groups: I. Receptor-mediated transcytosis through transferrin, insulin, and LDL receptors, II. Transcytosis through adsorption by means of electrostatic forces, III. Molecules such as glucose and amino acids serve as carriers for transporting other molecules (5, 6).

Physiological stability and accurate targeting of molecular targets are enhanced by the ability of QDs to be modified on their surfaces via ligand, peptide, or antibody conjugation (6). On the other hand, reduced neuroinflammatory responses and preserved BBB integrity, leading to improved safety profiles in *in vivo* studies, are achievable with biodegradable QDs (5). Also, the tunability of the QD emission spectrum via particle size results in higher quantum efficiency and photostability than those of conventional fluorophores (7). QDs are ideally suited for this purpose due to their high-resolution imaging of neural circuits, ability to track disease progression, and real-time

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measurement of treatment efficacy. To illustrate, beta-amyloid aggregates have been detected as an early biomarker of Alzheimer's pathology, and neuronal populations can be selectively illuminated with carbon QDs (CQDs)(8). Moreover, they can be multiplexed owing to their broad absorption spectrum, specific, size-dependent emission, and improved uptake of target molecules achieved through nitrogen doping (chemical modifications)(9).

Although QDs offer many benefits, their limitations remain a major challenge in clinical applications. As an illustration, one of the heavy metal elements (cadmium) is potentially toxic, leading to the following effects: oxidative stress, neuronal damage, and electrophysiological dysfunction (7, 10). However, the high surface energy of QDs promotes aggregation, thereby altering their stability and biodistribution. To address these biocompatibility issues and enable their clinical use in neurological disorders, researchers have employed advanced strategies such as core-shell designs, surface functionalization, and PEGylation (7, 11). The purpose of this review is to offer a detailed summary of the current developments in the design and use of targeted QD-based platforms to detect and possibly treat neurodegenerative diseases in early stages. Lastly, the review emphasizes the current issues and outlook on the clinical translation of QD-based technologies.

Methods

A total of 23 studies in PubMed, Scopus, and Web of Science databases published between 2000 and 2025 resulted in the identification of diagnostic or therapeutic uses of targeted QDs in neurodegenerative diseases. The important search terms included: targeted QDs, quantum dot imaging, nanotherapy, neurodegeneration, and particular disorders (e.g., Alzheimer's disease or Parkinson's disease). Original English-language (peer-reviewed) articles featured studies of functionalized QDs *in vitro, in vivo,* or in early translation models. Articles deemed irrelevant were removed, followed by filtering of titles and abstracts, and finally full-text filtering. The data extracted were QD formulation, targeting strategy, experimental model, and dose or imaging parameters, observed diagnostic or therapeutic outcomes, and limitations.

QDs as next-generation nanoplatforms in neurodegenerative disease research

QDs are increasingly employed in nanotechnology-based approaches as multifunctional theranostic platforms for neurodegenerative diseases.

Top-down and bottom-up were the primary methods of QD preparation (Figure 1). The top-down approach is the gradual breakdown of bulk semiconductor materials into nanoscale QDs, also known as laser ablation. The self-assembly of atomic or molecular precursors (including hydrothermal, microwave-assisted, and biosynthetic methods for QDs by bacteria or plants) is called the bottom-up method for QDs. Both synthesis pathways play a significant role in determining the distinct physicochemical characteristics of materials for biomedical and drug-delivery applications. Most traditional metal-based QDs (where the cores are made of heavy metal, e.g., cadmium (Cd) or lead (Pb)) surrounded by a semiconductor shell are also a type of nanoceramic semiconductor particle used in biomedical applications, including tumor imaging and therapy (12, 13). Moreover, oxide-based QDs have become an attractive subclass of nanoceramics because of their inorganic, nonmetallic crystalline lattice, robust ionic/covalent bonding, and optical property modulation. These structural characteristics result in high optical stability, biocompatibility capabilities, and controlled emission profiles. However, their cores can still pose problems regarding heavy-metal ion release, cytotoxicity, and even stability under physiological conditions due to their metal- or oxide-based nature (12). To overcome these deficiencies, new-generation QDs were developed to preserve desirable optical and electronic properties while reducing toxicity. Recent classes of QDs, such as CQDs, graphene QDs (GQDs), black phosphorus QDs (BPQDs), and perovskite QDs (PQDs), have provided specific physicochemical and biological properties that can be exploited to develop new diagnostic and therapeutic modalities (Figure 1). Physicochemical factors (particle size, surface charge, hydrophilicity, and protein halo formation) can influence the interaction of QDs with biological barriers and neural tissues. Studies have shown that QDs smaller than 10 nm (especially carbon-, graphene-, and ZnO-based systems) can

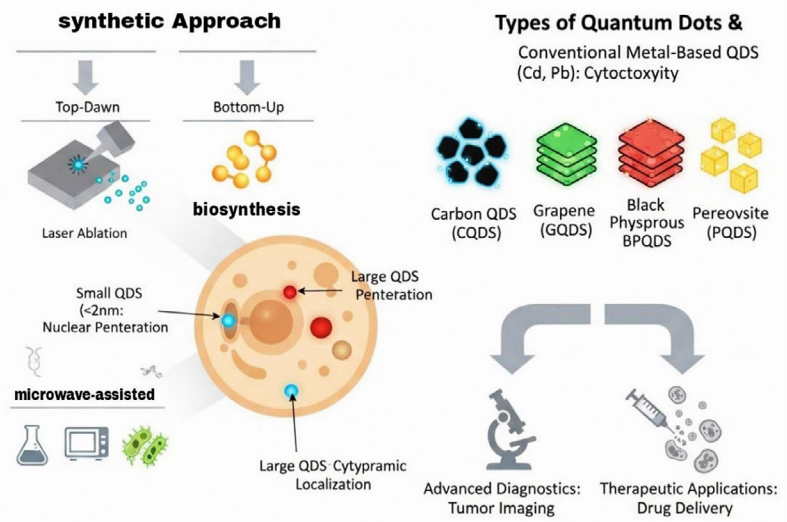

Figure 1. Schematic summary of top-down and bottom-up quantum dot synthesis, classification with toxicity considerations, nanoparticle intracellular penetration and localization, and translational applications in imaging and drug delivery

cross the blood–brain barrier (BBB) via receptor-mediated transcytosis pathways, with efficiency varying with surface functionalization (14).

For instance, surface-modified QDs functionalized with PEG, peptides, or polysaccharides exhibit enhanced circulation time and reduced opsonization, facilitating accumulation in brain tissues. However, non-targeted QDs may exhibit non-specific biodistribution and partial clearance via hepatic and renal pathways, thereby limiting their stability and retention in the central nervous system (15).

Importantly, *in vivo* behavior is also influenced by dynamic protein corona formation, which can alter the effective size and surface chemistry of QDs, thereby modulating their binding affinity and cellular uptake. Reported binding interactions between QDs and biomolecular targets are typically driven by electrostatic forces, hydrogen bonding, hydrophobic interactions, and π-π stacking (for graphene-based QDs), rather than covalent bonding, leading to reversible and dynamic association–dissociation processes in physiological environments (16).

Once in the central nervous system, these nanostructures interact with pathological biomarkers such as amyloid-β, tau, and α-synuclein through a combination of electrostatic interactions, hydrogen bonding, π-π stacking, and coordination bonding, leading to inhibition of protein aggregation, modulation of oxidative stress, and neuronal protection (17).

QDs are very sensitive to their size in the intracellular distribution. The crossing of biological barriers within the cell determines their intracellular fate and, in turn, their ultimate localization (18, 19). Table 1 summarizes a comparison of the major physicochemical and biocompatibility properties of various QDs, including variations in source materials, crystal structures, toxicity, photostability, and biomedical uses.

Targeted QDs for the diagnosis and treatment of neurodegenerative diseases

Recent advancements in QD synthesis, surface engineering, and biocompatibility have greatly broadened the biomedical applications of QDs beyond classic imaging. Neurodegenerative diseases like Parkinson's and Multiple Sclerosis can be treated early, as core molecular pathologies such as toxic protein aggregation, oxidative stress, neuroinflammation, and mitochondrial dysfunction are early manifestations of the disease. Figure 2 provides a schematic overview of the pathogenesis

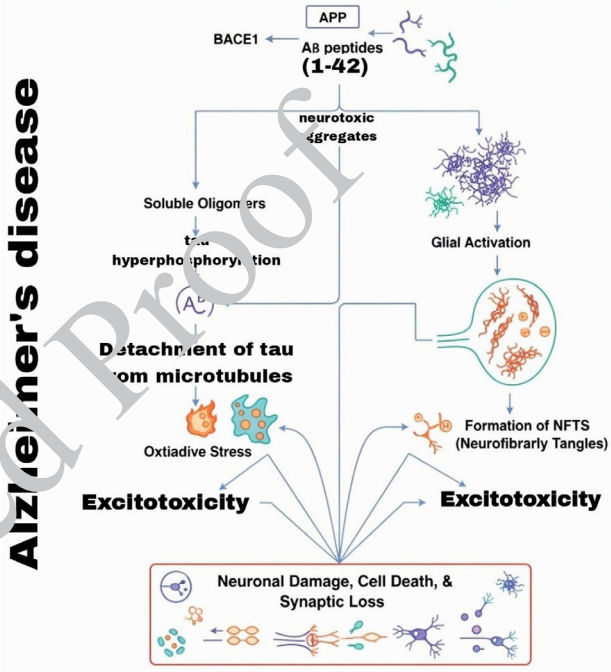

Figure 2. Schematic representation of Alzheimer's disease pathogenesis

Table 1. Comparative table of different advanced quantum dots (QDs)

QD Type	Source Material	Crystal Structure	Typical Size	Biocompatibility	Potential Toxicity	Photoluminescence (PL)/ Photostability	Bio-applications	Synthesis Cost	Environmental Stability	Ref.
CQDs	Organic compounds (e.g., citric acid, sugars)	Amorphous or quasi-crystalline	2-10 nm	Very high, non-toxic	Very low	Strong and stable/ Very high	Bioimaging, biosensing, and drug delivery	Very low	High	(20)
GQDs	Graphite and graphene derivatives	Crystalline with a planar, layered structure	1-20 nm	High, depending on the synthesis method	Dependent on the synthesis method	Stable, dependent on layer count/ Moderate to high	Imaging, drug delivery, sensors	Moderate	High	(21)
ZnO QDs	Zinc oxide (ZnO); abundant, low-cost, and eco-friendly	Wurtzite (hexagonal) structure.	2-10 nm	Generally good; improves with surface modification.	Low; possible Zn^{2+} ion-related toxicity at high concentrations.	Strong PL[a] from the UV[b] to the visible range; good photostability; defect states contribute to the visible emission.	Bioimaging, biosensing, drug delivery, and photocatalysis.	Very low	Moderate; stable under ambient conditions but less stable in acidic or humid environments (can be improved by surface coating)	(22)
BPQDs	Black phosphorus (a stable allotrope)	Layered crystalline with a puckered, anisotropic structure	1-10 nm	Good, as phosphorus is a native element in the body	Low, but prone to oxidation in air	Very strong (often burst-like)/ Relatively low (due to oxidation sensitivity)	Imaging, cancer therapy, sensors	High (due to expensive precursor material)	Lower (requires a protective coating in ambient conditions)	(23)
PQDs	Lead halide perovskites (e.g., $CsPbX_3$, X = Cl, Br, I).	ABX_3 perovskite lattice; (Cubic / Tetragonal / Orthorhombic)	QD regime	Low Pb[f] content limits biological use.	Moderate to high due to lead (Pb).	High PLQY,[c] tunable visible emission; stability under light/moisture limited.	Rare; mostly optoelectronics	Moderate; solution-based colloidal synthesis	Poor; sensitive to moisture, heat, and light; needs surface passivation	(24)
CdSe QDs	Cadmium selenide (CdSe), II–VI semiconductor	Zinc-blende (Cubic) or wurtzite (Hexagonal); often core/shell (CdSe/CdS)	~2-10 nm	Low Cd toxicity limits biological use.	High due to cadmium content.	High PL, tunable visible emission; stability improved with shell/ligands.	Limited (imaging/sensing); mainly optoelectronics.	Moderate; hot-injection and colloidal methods	Moderate; surface passivation enhances stability	(25)
MoS_2 QDs	Molybdenum disulfide (MoS_2), a 2D layered TMD[e]	Mainly 2H hexagonal phase; occasional 1T metallic phase may appear depending on synthesis	~2-6 nm	Generally good to excellent; low cytotoxicity, especially when surface-passivated (PEG/PVP)[d]	Low, but can increase due to: surface defects, ROS generation at high doses, Mo-ion release, or long-term accumulation	Strong PL (blue, green, 420–530 nm); photostability moderate to good, can decrease under long UV exposure	Fluorescence imaging, biosensing, drug delivery, photothermal therapy, antioxidation, anti-aggregation (Aβ in Alzheimer's), photoacoustic imaging	Low to moderate	Good aqueous stability, resistant to physiological pH; the surface can oxidize over time under strong UV or oxidative conditions	(26)

[a] photoluminescence (PL), [b] UV spectroscopy (UV), [c] photoluminescence Quntum Yield (PL QY), [d] Polyetylen glaycol/polyvinylpyrrolidone (PEG/PVP), [e] Transition Metal Dichalcogenide (TMD), [f] lead (Pb)

of Alzheimer's disease: APP cleavage to Aβ leading to neurotoxic aggregates and soluble oligomers that induce tau hyperphosphorylation, glial activation, and NFT formation, which, through oxidative stress and excitotoxicity, result in neuronal damage, cell death, and synaptic loss (27).

Similarly, oxidative damage, demyelination, and microglial activation are the initial stages observed in MS before neurological deficits, underscoring the significance of early molecular treatment. Traditional pharmacotherapies, including Levodopa in PD, do not slow the course of the disease and have serious long-term side effects, including hallucinations and cognitive impairment (23, 28). The pathogenesis of Parkinson's disease can be summarized as follows (Figure 3): αsynuclein aggregation into toxic oligomers and fibrils, Lewy body formation and transsynaptic spread, selective degeneration of substantia nigra dopaminergic neurons, consequent dopamine depletion, and resultant cardinal motor symptoms (bradykinesia, rigidity, resting tremor).

Within this context, targeted QDs offer unique opportunities to address diagnostic and therapeutic challenges through their tunable physicochemical properties, superior optical performance, and capacity for targeted delivery across the blood–brain barrier (BBB)(8, 9, 28).

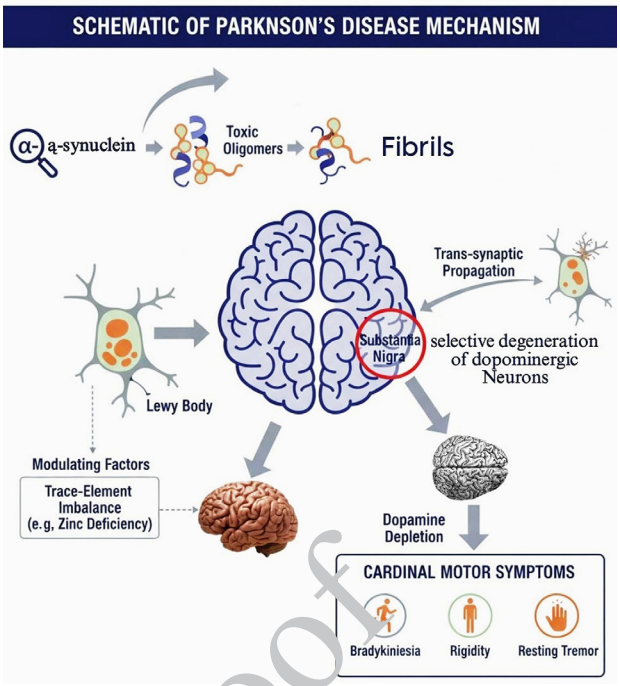

Figure 3. Schematic representation of Parkinson's disease pathogenesis

Targeted carbon QDs (CQDs)

CQDs have become the best fluorescent probes because of their non-toxicity, high quantum yield, excellent photostability, and low production cost, which make them appealing for biosensing and biomedical studies. The sensitivity of their intrinsic fluorescence enables a variety of diagnostic uses, including biosensing, pharmaceutical assays, and metal ion detection, such as copper chelation.

CQDs are quasi-spherical nanoparticles (<10 nm) with sp^2-hybridized carbon cores and crystalline or amorphous structures, functionalized with functional groups (carbonyl, hydroxyl, amine) to enhance dispersibility and biocompatibility (29, 30). Table 2 highlights the latest developments in the design and use of engineered CQDs for diagnostic imaging, therapy, and combined theranostic approaches in the treatment of neurological disorders.

Table 2. Provides a concise overview of recent research on engineered carbon QDs (CQDs) applied in diagnostic, therapeutic, and theranostic approaches for neurological disorders

		Targeted QDs	Disease	Experimental model	Results	Limitations	Ref
Applications	Diagnosis	N-doped carbon quantum dots (N-CQDs)	Neurotransmitter dysregulation / GABA[a] monitoring	*In vivo* (zebrafish brain: telencephalon and optic tectum) and *in vitro* cellular models	Detection limit ~0.16 μM; real-time monitoring; selective turn-off fluorescence response; biocompatible and optically stable	No human validation; long-term *in vivo* stability unknown	(8)
		Sulfur- and nitrogen-doped carbon quantum dots (S, N-CDs)	Parkinson	*In vitro* in aqueous solutions and real samples (drugs and artificial serum). (Fluorescence spectroscopy, smartphone-based fluorimeter)	High sensitivity, selective fluorescence quenching by L-DOPA[b]	No biological or *in vivo* validation; analytical proof-of-concept only	(31)
		N-doped CQDs from fruit peel; fluorescence quenching for dopamine detection	Parkinson	*In vitro* assays; spiked sample tests	High sensitivity and selectivity; 98-103% recovery	No *in vivo* data; no biological targeting; possible interference	(29)
	Therapeutic	Carbon quantum dots (CQDs) with surface functional groups enabling interaction with amyloidogenic peptides	Alzheimer	*In vitro*: β-amyloid (Aβ) and α-synuclein fibril assays; SH-SY5Y neuronal cells	Disaggregated Aβ[c] and α-syn fibrils; reduced protein aggregation; maintained neuronal viability (~85%); decreased ROS and lipid peroxidation	Only *in vitro* studies; no BBB[c] or *in vivo* data; lack of long-term stability and pharmacokinetic analysis	(32)
		Selenium-doped carbon quantum dots (Se-CQDs) mimicking large amino acids for multi-target AD therapy	Alzheimer	*In vitro* Aβ and antioxidant assays; PC12 neuronal cells; APP/PS1 transgenic mice	Inhibited Aβ aggregation, reduced ROS, restored metal ion balance, improved memory in mice, and had low toxicity	No long-term safety data; unclear BBB transport; limited clinical translation	(33)
	Theragnostic	Macrophage membrane–encapsulated nitrogen-doped carbon quantum dots (N-CQDs) enabling BBB penetration and Aβ-targeted delivery	Alzheimer	*In vitro* Aβ and ROS assays; PC12 neuronal cells (up to 200 μg/mL); *in vivo* APP/PS1 transgenic mice (5 mg/kg)	Inhibited Aβ aggregation, restored Cu^{2+}/Zn^{2+} balance, reduced ROS, improved cognition in mice; high biocompatibility (>90% cell viability)	Complex synthesis; incomplete pharmacokinetic and long-term safety data; limited scalability for clinical translation	(5)
		Verapamil-loaded carbon quantum dots, hyaluronic acid-coated	LPS-induced neurotoxicity in rats (Alzheimer's)	*in vitro:* human neuroblastoma *In vivo:* LPS[d]-treated rats	Improved cognition, reduced neuroinflammation and oxidative stress, enhanced neuronal gene expression	Long-term safety, biodistribution, and clearance not fully assessed; translation to humans pending	(34)

[a] γ-aminobutyric acid (GABA), [b] Levodopa is the main drug for treating Parkinson's disease (L-DOPA), [c] blood–brain barrier (BBB), [d] Lipopoly saccharide (LPS), [e] α-synuclein and β-amyloid (Aβ)

Diagnostic applications

CQDs are highly sensitive nanosensors and imaging probes that detect molecular and cellular changes with high accuracy. As an example, Raut *et al.* developed a new *in vivo* biosensing system based on nitrogen-doped carbon QDs (N-CQDs) to detect γ-aminobutyric acid (GABA), a vital neurotransmitter in inhibitory signaling. The synthesis of the N-CQD nanoparticles was performed via controlled carbonization and nitrogen doping. The QDs exhibited high fluorescence, which was selectively suppressed (turn-off) upon interaction with GABA, enabling sensitive detection. The biosensor was tested in cellular models and zebrafish brain regions (telencephalon and optic tectum), demonstrating a detection limit of ~0.16 μM and the ability to monitor in real time. The article demonstrates that N-CQDs have several benefits as *in vivo* neurochemical sensors, including high biocompatibility, optical stability, and rapid response. Nevertheless, there are still constraints of translation to higher-order animals or humans, the potential effect on more intricate biological matrices, and the long-term safety and toxicity of QDs *in vivo*. In general, this paper shows the promise of N-CQDs as effective nanoscale fluorescent sensors for the selective, sensitive, and real-time detection of neurotransmitters in living organisms (8).

The intense fluorescence of CQDs can be achieved through heteroatom doping. Sulfur- and nitrogen-doped CQDs (S, N-CQDs), in particular, have demonstrated high efficiency as probes for detecting L-DOPA (31). Hemmati *et al.* prepared S, N-CQDs via a green synthesis method as fluorescent nanosensors for detecting L-DOPA, a major therapeutic agent in Parkinson's disease. The S, N-CQDs also showed strong blue fluorescence, which was selectively suppressed by L-DOPA, thereby enabling quantification of the compounds using a smartphone-based fluorimeter in a sensitive, portable mode. Not only does this study outline the diagnostic capabilities of engineered CQDs as real-time drug biosensors for neurological diseases, but it also indicates future theranostic opportunities owing to the high biocompatibility, fluorescence stability, and surface functionality. No therapeutic or biological assays were performed; however, this limited the study to an analytical proof of concept (31).

Additionally, Han *et al.* describe a green synthesis pathway for nitrogen-doped carbon QDs (N-CQDs) using waste fruit peels and demonstrate their use as a fluorescent sensor for the selective, sensitive detection of dopamine (DA). The N-CQDs exhibit high blue emission and fluorescence quenching with the dopamine, thus allowing it to be quantitatively sensed in aqueous conditions as well as in spiked real samples with high recovery (≈98-103%) and low relative standard deviations (2-6%), suggesting the possibility of low-cost, point-of-care dopamine assays. It does not include surface functionalization for targeted *in vivo* brain delivery, nor does it evaluate performance in complex biological fluids or physiological models. These limitations highlight the need for additional studies to assess its performance in real-world physiological environments before considering clinical translation (29).

In another study, N-CQDs showed a considerable dose-dependent decrease in amyloid fibril aggregation in thioflavin T (ThT) assays, and dynamic light scattering demonstrated a maximum decrease in amyloid aggregate size of fivefold (35).

Therapeutic strategies

CQDs have high therapeutic potential owing to their biocompatibility, surface functionalization, and ability to cross the BBB (36).

Guerrero *et al.* investigated the intrinsic therapeutic potential of non-targeted approaches of CQDs in the treatment of amyloid-associated neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases. The surface oxygen-functional groups (-COOH, -OH, and C=O) were direct forces of interaction with amyloidogenic proteins. These groups facilitated hydrogen bonding, π-π stacking, and electrostatic interactions with the β-sheets of β-amyloid (Aβ) and α-synuclein, thereby inhibiting the nucleation and growth of fibrils and stimulating the disaggregation of existing aggregates.

A significant decrease in fibrillar structures and stabilization of non-toxic amorphous species were confirmed in an *in vitro* study using spectroscopic and imaging analyses, such as Thioflavin T fluorescence, circular dichroism, and AFM. In addition, CQD therapy maintained neuronal viability (>85% SH-SY5Y cells) by inhibiting the formation of reactive oxygen species (ROS) and lipid peroxidation, thereby exerting antioxidant effects. Although these results are encouraging, the experiment is limited to *in vitro* tests and does not include BBB permeability or *in vivo* testing. On the whole, this literature highlights the non-targeted yet functionally active role of surface-rich CQDs as intrinsic nanochaperones that can reduce amyloid aggregation and oxidative neurotoxicity through surface-mediated molecular interactions, rather than engineered targeting systems (32).

Selenium-doped carbon QDs (Se-CQDs) are another promising multifunctional therapeutic platform for treating Alzheimer's disease (AD). In contrast to traditional selenium nanoparticles (Se-NPs), which are limited by their larger size and antioxidant properties alone, Se-CQDs combine several therapeutic functions into a single nanosystem. The rationally designed Se-CQDs in the study by Zhou *et al.* were formulated as large amino acid-like molecules that could regulate metal ion homeostasis, prevent β-amyloid (Aβ) aggregation, and eliminate reactive oxygen species (ROS). Their multifunctionality was demonstrated by experimental studies of Aβ aggregation *in vitro* and antioxidant studies in neuronal cells (PC12) and APP/PS1 transgenic mouse models. The results showed an effective way to reduce Aβ plaque deposition, mitigate oxidative stress, safeguard neuronal integrity, and enhance cognitive function without apparent systemic toxicity. This multimodal therapeutic approach offers a potential means to treat the complex, multifactorial pathology of AD. However, some long-term biocompatibility, BBB delivery, and translational prospects still need to be demonstrated before clinical implementation (33). Though promising, there are still some limitations. Even though CQDs can be activated by light to destabilize β-amyloid, the superficial penetration of blue/UV light into the brain limits their therapeutic efficacy in deep brain areas. Strategies being investigated include the creation of red/NIR-responsive CQDs or the use of implantable optical devices (e.g., fiber optics) to enable much deeper activation (36).

Theranostic application

CQDs are one of the best theranostic agents to handle

owing to their dual diagnostic and therapeutic properties. They have intrinsic fluorescence to visualize biomarkers and cellular processes in real-time and to detect biomarkers, and their therapeutic roles include photothermal therapy, ROS scavenging, and amyloid-β inhibition (5, 37). As an example, Near-infrared (NIR)-activated carbon QDs (CQDs) have become promising theranostic agents, capable of disrupting amyloid aggregates and enabling real-time tracking of biodistribution and treatment response, thereby bridging diagnosis and treatment in a single nanoplatform. Based on this, Ye *et al.* developed a biomimetic macrophage membrane-encapsulated nitrogen-doped carbon quantum dot (N-CQD) nanosystem to target AD treatment. This was due to the inherent inflammation-homing effect conferred by the macrophage membrane coating, which increased the rate of BBB penetration and localization around β-amyloid (Aβ) plaques. A set of detailed *in vitro* experiments showed that N-CQDs were capable of regulating the homeostasis of Cu^{2+} and Zn^{2+} and inducing photothermal disaggregation of ABB fibrils during NIR laser irradiation (808 nm, 1.0 W/cm^2). The biocompatibility of PC12 neuronal cells was confirmed by cytotoxicity and neuroprotective assays, which demonstrated suitable cell viability (>90%) up to 200 μg/ml. In addition, *in vivo* analyses of APP/PS1 transgenic AD mice demonstrated that Aβ plaque burden, oxidative stress, and spatial learning and memory performance significantly improved after intravenous injection of N-CQDs (5 mg/kg). Together, the results underscore the dual metal-regulating and photothermal therapeutic effects of the nanosystem, which can be employed as a powerful approach to treating the multifactorial pathology of AD. However, the method has problems with synthetic complexity, incomplete pharmacokinetic profiling, and biosafety evaluation over long periods, delaying clinical translation (5).

Moreover, Elberri *et al.* developed a new type of verapamil-loaded carbon QDs (VCQDs) surface functionalized with hyaluronic acid to deliver the drug to the brain in a targeted manner, thereby allowing controlled release into neurons and injured areas. The hyaluronic acid surface enables the identification of specific receptors on brain cells, including CD44, and inflammatory pathways, thereby promoting biocompatibility and targeted delivery while avoiding off-target distribution. The effectiveness of this targeted strategy was demonstrated in *in vivo* models of LPS-induced neurotoxicity, which showed improved cognitive performance, reduced neuroinflammation, and alleviated oxidative stress (reduced ROS and MDA, increased GSH). Mechanistically, VCQDs dampened inflammatory cytokines (TNF-α, IL-6, NF-κB, TLR4) and modulated neuronal gene expression (CREB, CRTC3, BDNF, CCO), and the CQD platform enabled controlled release of verapamil. The particles were about 7.5 nm in diameter, and the dose administered *in vivo* was 3 mg of verapamil per 1 mL of VCQD, thereby facilitating particle accumulation in the brain and reducing side effects. This paper presents a theranostic CQD-based platform for the delivery of targeted, controlled drugs for neurodegenerative diseases (34).

Engineered graphene QDs (GQDs)

GQDs are a unique type of QDs consisting of a planar, sheet-like network of graphene, with lateral dimensions exceeding 100 nm and fewer than ten graphene layers (9). They are crystalline and have a layered structure, which confers on them better photostability, higher electrical conductivity, and quantum properties than those of amorphous carbon dots (9). GQDs have carboxyl groups on their surfaces, enabling easy conjugation with biological ligands, drugs, or other nanomaterials (9). They can be further heteroatom-doped (e.g., N, B, S, P) to alter their physicochemical and biological properties (9). According to biocompatibility studies, GQDs reduce oxidative stress markers by up to 25%, indicating a promising biological profile (7). GQDs can enter the brain via endocytic and exocytic routes and are gradually taken up and released by brain cells, underscoring their potential for treating neurodegenerative diseases (38, 39). There was no evidence of loss of dopaminergic neurons, glial overactivation, abnormal behavior, or organ toxicity with long-term administration of PD models, which demonstrated low long-term toxicity and effective renal clearance (39). Their planar, quasi-two-dimensional structure also offers a high surface area to load drugs, allowing them to control dosage and release drugs precisely (7). The design and implementation of GQDs engineered to serve as diagnostic or therapeutic imaging agents, or as part of an integrated theranostic approach to neurological diseases, are summarized in Table 3.

Diagnostic applications

The nitrogen-doped NGQDs showed greater efficiency than their non-doped counterparts and conventional nanoparticles in terms of cytotoxicity and biocompatibility, making them reliable nanoprobes in AD-related studies (7, 9). The high optical performance, increased fluorescence, and quantum yield of nitrogen-doped NGQDs make them highly suitable for brain-targeted imaging applications (40). Researchers developed NGQDs with a size of 3-5 nm and used them as fluorescent nanoprobes to study their interactions with anti-Alzheimer drugs and the enzyme acetylcholinesterase (AChE). The NGQDs (at concentrations of 10-50 μg/ml) were conducted in their entirety as *in vitro* spectroscopic assays. They demonstrated fluorescence quenching in the presence of AChE activity, which was later restored by adding a range of anti-AD compounds, including tacrine, donepezil, and recently synthesized analogs (PC-25, PC-37, PC-48). The results showed the best inhibitory capacity with 85-96 percent signal recovery, and a limit of detection (LOD) of 2.87 mM. It was demonstrated that synthesized NGQDs have potential as diagnostic and drug-screening tools, as they can track enzyme inhibition via fluorescence changes in Alzheimer's research. Nevertheless, as cellular or *in vivo* validation of the results has not been established, the study is limited to a diagnostic (non-therapeutic) model, and additional studies are necessary to determine the level of biocompatibility and therapeutic translation (40).

Therapeutic strategies

GQDs are considered among the most promising neuroprotective nanomaterials due to their distinctive physicochemical characteristics and affinity for misfolded proteins. They have direct protective effects that prevent the aggregation of α-synuclein and β-amyloid (Aβ) peptides, thereby preventing the development of neurotoxic fibrils (1). Moreover, GQDs dose-dependently inhibit intracellular

Table 3. Provides a concise overview of recent research on engineered graphene QDs (GQDs) applied in diagnostic, therapeutic, and theranostic approaches for neurological disorders

		Targeted QDs	Disease	Experimental model	Results	Limitations	Ref
Applications	Diagnosis	Nitrogen-enriched graphene quantum dots (NGQDs), average size 3-5 nm	Alzheimer	*In vitro* spectroscopic assay, fluorescence-based enzyme inhibition test (no cells or animals used)	NGQDs' fluorescence quenched by AChE[a] activity and restored by anti-AD[b] drugs PC-37 exhibited the strongest AChE inhibition and fluorescence recovery (85-96% signal restoration) Demonstrated high sensitivity and specificity for AChE-drug interaction detection	No cellular or *in vivo* validation. Lacks biocompatibility and toxicity assessment. Limited to molecular-level diagnostics, not therapeutic or theranostic applications	(40)
	Therapeutic	Biomimetic graphene nanoparticles (cell membrane-coated reduced graphene oxide nanosheets -CM-GNPs)	Alzheimer	*In vitro*: tau-overexpressing neuronal cells; *In vivo*: tau transgenic mouse model	Blocked intercellular tau propagation; reduced hippocampal tau load; preserved synaptic function; improved cognitive behavior in mice	Limited PK/toxicity data; complex synthesis; no long-term immune or degradation assessment	(38)
		Graphene quantum dots (GQDs) with abundant oxygen-containing surface groups	Parkinson	*In vitro*: primary midbrain neuronal cultures; *In vivo*: mice injected with α-syn pre-formed fibrils (PFFs)	Disaggregation of α-syn fibrils; protection of dopaminergic neurons; reduction in Lewy-like inclusions; improved motor performance; BBB[c] permeability confirmed	Lack of long-term pharmacokinetic data; limited toxicological evaluation; scaling and reproducibility for clinical translation remain unresolved	(39)
		Graphene oxide quantum dots (GOQDs) with intrinsic catalase-like nanozyme activity	Alzheimer	*In vitro*: PC12 and Neuro-2a neuronal cells; *In vivo*: Kunming mic	GOQDs (25-200 μg/mL *in vitro*; 2-10 mg/kg *in vivo*) reduced ROS via H_2O_2[d] decomposition, prevented neuronal apoptosis, alleviated oxidative stress, and improved cognitive performance without notable toxicity	No pharmacokinetic or long-term toxicity data; BBB transport efficiency not quantified; lack of diagnostic or imaging functionality	(41)
	Theragnostic	Two sizes of graphene quantum dots (GQD7 and GQD28) were investigated for binding to Tau monomers, straight filaments (SFs), and paired helical filaments (PHFs)	Alzheimer	In silico docking and molecular dynamics (MD) simulations; no *in vitro* cell or *in vivo* animal experiments reported	GQD28 showed high affinity to the PHF6 hexapeptide region of Tau; GQD7 targeted both PHF6 and PHF6* regions; identified key binding sites that may be useful for detecting, preventing, or disassembling Tau aggregates.	Study is purely computational (no experimental validation); no dose, cell line, animal model, or therapeutic/diagnostic *in vivo* data; translation to real biological systems remains speculative	(42)
		Nitrogen-doped graphene quantum dots (NGQDs), covalently and non-covalently conjugated with Memantine	Alzheimer	*In vitro* cellular assays (astrocytes for Ca^{2+} influx; SH-SY5Y and neuroglial cultures for viability); *in vitro* BBB model using endothelial cell monolayers	Inhibited NMDA-induced Ca^{2+} influx; prevented Aβ fibrillogenesis; crossed BBB (P_app≈75%); maintained astrocyte viability; strong fluorescence for bioimaging	Primarily *in vitro*; no *in vivo* pharmacokinetic or neurobehavioral validation; incomplete long-term toxicity and immune profiling	(43)

[a] acetylcholinesterase (AChE), [b] anti-Alzheimer 's disease (anti-AD), [c] blood–brain barrier (BBB), [d] Hydrogen peroxide (H_2O_2)

ROS production, thereby decreasing oxidative stress and reducing neuronal dysfunction and apoptosis (1, 44).

Another line of research, based on these findings, focused on biomimetic graphene nanoparticles (GNPs), which prevent the diffusion of one of the pathological processes in AD and other tauopathies: the tau protein. To create a camouflaged nanoplatform (CM-GNPs) that mimics neuronal interactions with the natural cell surface, the scientists coated the reduced graphene oxide (rGO) nanosheets with neuronal cell membrane vesicles. The resulting CM-GNPs (average size of approximately 80 nm) exhibited high colloidal stability and biocompatibility. *In vitro* experiments in tau-overexpressing neuronal cultures with CM-GNPs prevented the uptake and intercellular transfer of pathological tau aggregates as visualized by fluorescence microscopy. *In vivo* delivery in tau-transgenic mice revealed decreased tau seeding and propagation throughout the hippocampus and cortex, resulting in enhanced synaptic health and memory function. Mechanically, the graphene core was used as an adsorption interface for misfolded tau via π–π stacking, and the biomimetic membrane coating was used to deliver and to avoid immune response (38). Overall, CM-GNPs were shown to be curative nanointerventions that inhibit the prion-like propagation of tau pathology. However, the lack of complete pharmacokinetic characterization, the lack of information on long-term toxicity, and the nature of membrane-based fabrication can pose challenges for mass translation.

In parallel with these advances, Ysselstein *et al.* investigated the therapeutic potential of GQDs to target α-synuclein aggregation, a central pathological hallmark of PD. GQDs are small (less than 10 nm laterally) and richly endowed with carboxyl and hydroxyl groups, which confer a high affinity of these compounds toward α-syn fibrils through π–π and hydrogen-bond interactions. *In vitro* experiments revealed that GQDs could disrupt pre-existing α-syn fibrils converting them into non-toxic amorphous species and thereby alleviating cytotoxicity in primary midbrain neuron cultures. *In vivo* delivery in mice injected with pre-formed α-syn fibrils led to a considerable decrease in Lewy-like inclusions, improved dopaminergic neuronal survival, and reversal of motor deficits. Significantly, GQDs crossed the BBB without causing inflammation or systemic toxicity. Taken together, these results identify GQDs as effective nanotherapeutics capable of physically remodeling amyloid fibrils and alleviating PD pathology. However, insufficient long-term pharmacokinetic and biodistribution data, the unclear metabolic fate of GQDs in the CNS, and the need to optimize clinical dosing are the main limitations (39).

Lastly, Ren *et al.* studied the use of graphene oxide QDs (GOQDs) as a versatile therapeutic nanomaterial to reduce oxidative neurotoxicity. The study combined *in vivo* and *in vitro* studies to evaluate the neuroprotective potential of GOQDs via their inherent catalase-like nanozyme activity. GOQDs at 25-200 μg/ml exhibited high biocompatibility and decomposed hydrogen peroxide (H_2O_2) in neuronal cell models (PC12 and Neuro-2a), thereby suppressing the accumulation of intracellular ROS and inhibiting apoptosis. Moreover, when systemically administered in Kunming mice, 2-10 mg/kg doses of GOQDs mitigated oxidative stress and enhanced behavioral and cognitive functions, proving the therapeutic benefits of GOQDs *in vivo*. Mechanistically, these nanostructures controlled oxidative metabolism and augmented endogenous antioxidant defense. Although the results are quite convincing for the neuroprotective role of GOQDs, the lack of thorough pharmacokinetic information, the description of BBB transport, and long-term toxicity prevent the immediate applicability of these compounds in

humans. Overall, this research highlights the potential of graphene-based QDs as redox-controlling nanoagents in the treatment of neurodegenerative diseases (41).

The new evolution of graphene-based quantum nanomaterials is driven by their high therapeutic potential for neurodegenerative diseases. *In vitro* and in vivo, GQDs can disperse α-synuclein and tau fibrils, prevent β-amyloid aggregation, eliminate free radicals to reduce oxidative stress, restore neuronal integrity, and inhibit disease progression in the brain. In studies, multi-target neuroprotection (improving calcium homeostasis, dopaminergic survival, and cognitive recovery) has been achieved using MABM-GQDs, biomimetic GNPs, nitrogen-doped GQDs, and GOQDs. Together, these findings enable us to suggest the use of graphene-derived QDs as multifunctional nanotherapeutics of antioxidant, anti-aggregative, and neurorestorative functions. Nevertheless, their clinical application as next-generation theranostic agents in neurodegenerative diseases is compromised by factors such as a paucity of pharmacokinetic data, limited long-term safety evaluation, and potential scalability issues in synthesis.

Theranostic applications

GQDs combine both therapeutic and diagnostic functionalities, making them ideal theranostic agents for neurodegenerative diseases. They enable simultaneous imaging, biomarker detection, and inhibition or disassembly of toxic protein aggregates (41, 44). By integrating drug delivery, reactive oxygen species (ROS) scavenging, and anti-amyloid activity, GQDs facilitate concurrent monitoring and treatment of neurodegenerative disorders (1, 28, 42). Their inherent biocompatibility, blood–brain barrier (BBB) permeability, and tunable surface chemistry further support precise and targeted theranostic intervention within the central nervous system (7, 39).

Building on these attributes, nitrogen-doped graphene QDs (NGQDs) have emerged as multifunctional theranostic nanoplatforms that integrate drug delivery, neuroprotection, anti-aggregation activity, and bioimaging capabilities (40, 43). NGQD-based fluorescence assays have been developed to evaluate anti-acetylcholinesterase (AChE) activity of novel Alzheimer's drug candidates, enabling rapid, low-cost, and non-toxic screening. Using this platform, three new compounds were tested, among which PC 37 was identified as the most potent inhibitor (40). Complementary BBB permeability studies using an *in vitro* xCELLigence model demonstrated that 71-75% of NGQDs and NGQD@Memantine conjugates successfully crossed the BBB, whereas NGQD-Memantine exhibited slightly lower permeability (~55%) due to higher drug loading. ABC transporter analysis indicated passive diffusion or endocytosis as the predominant translocation mechanism for NGQDs, while Memantine transport was associated with solute carrier proteins (SLC22A) (43). Collectively, NGQDs exhibit low toxicity, efficient BBB penetration, neuroprotective and anti-aggregation activity, and strong fluorescence for imaging. These characteristics position them as versatile nanoplatforms for CNS-targeted therapeutics and theranostic applications in neurodegenerative and oncological contexts (40, 43).

In a complementary in silico study, two distinct GQD models, GQD7 and GQD28, were computationally evaluated for their theranostic potential in AD through detailed docking and molecular dynamics simulations with tau monomers, straight filaments (SFs), and paired helical filaments (PHFs). The simulations revealed that GQD28 preferentially binds to the PHF6 hexapeptide region, while GQD7 interacts with both PHF6 and PHF6* motifs. These findings highlight specific binding interfaces that could enable both detection (diagnostic) and disruption (therapeutic) of tau aggregates, underscoring the dual functionality of GQDs. However, this work remains limited to computational modeling and lacks empirical *in vitro* or *in vivo* validation, as well as dosing, pharmacokinetic, or functional efficacy data. Thus, while mechanistically insightful, substantial experimental research is still needed to translate these computational predictions into practical diagnostic and therapeutic outcomes (42).

Expanding on this therapeutic concept, Gómez *et al.* designed nitrogen-doped graphene QDs (NGQDs) as an advanced nanosystem targeting multiple neurodegenerative mechanisms, including Ca^{2+} dysregulation, β-amyloid (Aβ) aggregation, and restricted brain drug delivery. NGQDs were synthesized via a microwave-assisted bottom-up route and conjugated with Memantine, a well-known NMDA receptor antagonist, through covalent (NGQD-Memantine) and non-covalent (NGQD@Memantine) strategies. Structural characterization confirmed nanometric dimensions (3.0±1.1 nm and 4.2±1.7 nm) and Memantine loadings of ~18±4% and ~30±2%, respectively. Functionally, NGQDs inhibited NMDA-induced Ca^{2+} influx in astrocytes, maintained cell viability up to ~100 µg/ml, and significantly suppressed $A\beta_{1\text{-}42}$ fibrillogenesis at ~22 µg/ml, producing oligomeric rather than mature fibrils. The *in vitro* BBB model exhibited high permeability (P_app ≈75%) and limited efflux, underscoring its potential for brain-targeted delivery. Moreover, the intrinsic fluorescence of NGQDs enabled visualization of cellular uptake and BBB traversal, confirming a combined therapeutic and diagnostic (theranostic) functionality. Nevertheless, as this work remains confined to *in vitro* assays, further *in vivo* studies are required to establish long-term biosafety, pharmacokinetics, and translational feasibility (43).

Targeted zinc oxide QDs (ZnO QDs)

Zinc, as an essential trace element with intrinsic antioxidant properties, further highlights the biomedical significance of engineered nano-ceramic zinc oxide QDs. Among various types of QDs, these ZnO QDs have garnered substantial attention in biomedical research due to their inorganic, crystalline nano-ceramic lattice, cost-effectiveness, low cytotoxicity, and excellent biocompatibility. Additionally, their pH-responsive degradability enables controlled dissolution in acidic microenvironments, such as tumor tissues or endosomal compartments, facilitating stimuli-responsive drug delivery and targeted therapeutic applications (28). Table 4 summarizes recent advances in the design and application of engineered ZnO-QDs for diagnostic imaging, therapeutic intervention, and integrated theranostic strategies targeting neurological diseases.

Diagnostic applications

Structurally, ZnO QDs possess a well-defined wurtzite crystal lattice confirmed by X-ray diffraction (JCPDS #00-036-1451). Surface modifications, including PEG, siloxane,

Table 4. Provides a concise overview of recent research on engineered zinc oxide QDs (ZnO-QDs) applied in diagnostic, therapeutic, and theranostic approaches for neurological

		Targeted QDs	Disease	Experimental model	Results	Limitations	Ref
Applications	Diagnosis	Zinc oxide quantum dots (ZnO-QDs) capped by (3-aminopropyl) triethoxysilane (APTES), water-soluble and fluorescent	Dopamine, an indirect biomarker for Parkinson's pathology	*In vitro* fluorescence assay: ZnO-QDs probe in buffer and serum samples	The fluorescence of ZnO-QDs was quenched by dopamine and showed high selectivity vs interfering species; good recoveries in serum (99-110%)	Analytical assay only, no cellular/neuro model, no therapeutic aspect, *no in vivo* validation, yield/size data limited	(45)
	Therapeutic	GSH/NGF[a]-functionalized ZnO QDs (ZnO@Polymer-NpG)	Parkinson	*In vitro*: SH-SY5Y, C6, PC12 cells; *In vivo*: MPTP-induced PD mice	Crosses BBB, silences SNCA gene, reduces ROS, restores TH levels, improves motor function	Complex synthesis, limited long-term biosafety, and no pharmacokinetic data	(28)
		Myco-fabricated zinc oxide nanoparticles (ZnO-NPs) synthesized via Aspergillus niger–mediated green method	Alzheimer	*In vivo* (mice), AD model induced by chronic $AlCl_3$ exposure	Significant reduction in acetylcholinesterase activity Decrease in malondialdehyde (MDA) and increase in glutathione (GSH) & antioxidant enzymes (SOD, CAT) Improved hippocampal histology and neuronal integrity Restoration of behavioral memory performance in treated mice	Lack of pharmacokinetic and biodistribution data No blood–brain barrier (BBB) permeability quantification Absence of long-term toxicity and dose–response evaluation	(46)
	Theragnostic	Polyglycerol-modified ZnO quantum dots (ZnO–HPG QDs) loaded with DOX	Cancer	*In vitro* (cellular assays: MCF-7[d] & HEK-293[c])	pH-responsive DOX[b] release (≈75% at pH 5.5); selective cytotoxicity to cancer cells; real-time fluorescent imaging	No *in vivo* validation; pharmacokinetics and long-term stability not assessed	(47)

[a] Glutathione/nerve growth factor (GSH/NGF), [b] Doxorubicin (DOX), [c] Human Embryonic Kidney 293 (HEK-293), [d] Human breast cancer cell line (MCF-7)

hyaluronic acid, folic acid, oleic acid, polystyrene, methyl methacrylate, poly(carboxybetaine methacrylate), and polyglycerol (PG), enhance dispersibility, biocompatibility, and targeted functionality of ZnO QDs in biological environments (47). In a foundational study, Zhao *et al.* developed water-soluble, APTES-capped ZnO QDs (ZnO-QDs) as a highly sensitive fluorescent probe for the neurochemical analysis of dopamine (DA). The ZnO-QDs exhibited a strong photoluminescence emission peak at ≈530 nm and were quenched upon the addition of DA in buffered solutions. Under optimal conditions, the probe achieved a linear detection range of 0.05-10 μM DA and an impressive limit of detection of approximately 12 nM, with recovery rates of 99-110% in serum samples. This demonstrates its strong potential for neurochemical diagnostics relevant to disorders where dopamine dysregulation plays a role. Nevertheless, the study is confined to an *in vitro* analytical format, lacking cellular, animal, or clinical validation, and does not report detailed nanoparticle size distribution (45).

Therapeutic strategies

In a landmark 2022 study, a brain-targeted ZnO quantum dot–based nanoplatform (ZnO@Polymer-NpG) was developed for the therapeutic modulation of Parkinson's disease (PD). The multifunctional ZnO-QDs, approximately 5-10 nm in diameter, were synthesized via a sol–gel process and subsequently functionalized with nerve growth factor (NGF) and glutathione (GSH) to enhance blood–brain barrier (BBB) permeability and neuroprotective efficacy. This nanoplatform was designed to deliver a gene-silencing construct targeting α-synuclein (SNCA) while simultaneously enabling fluorescence tracking via the intrinsic optical properties of ZnO-QDs (emission at ~530 nm). Both *in vitro* (PC12, SH-SY5Y, and C6 cells) and *in vivo* (MPTP-induced PD mouse) models demonstrated efficient neuronal uptake, significant SNCA down-regulation, reduced reactive oxygen species (ROS) levels, restoration of tyrosine hydroxylase (TH) expression, and improved motor coordination. The effective concentration window (0.25-3.0 mg/l Zn, with an optimal value of 0.75 mg/l) and the observed BBB penetration highlight the potential of ZnO-QDs as a theranostic nanocarrier for targeted neurotherapy. Despite these promising findings, the study acknowledges key translational challenges, including synthetic complexity, lack of long-term pharmacokinetic and immunogenicity data, and the need for further clinical validation to confirm safety and efficacy in human neurodegenerative disorders (28). Another study by Abd Elmoneim *et al.* developed a myco-fabricated zinc oxide nanoparticle (ZnO-NP) system using Aspergillus niger as a sustainable biological route. It evaluated its neuroprotective efficacy in an $AlCl_3$-induced mouse model of AD. The biosynthesized ZnO-NPs, with an average diameter of 20-30 nm, were administered orally at a dose of 10 mg/kg/day for 21 days, leading to a marked reduction in acetylcholinesterase activity, amelioration of oxidative stress biomarkers, and restoration of hippocampal neuronal architecture. Behavioral tests confirmed significant cognitive improvement in treated mice, demonstrating the nanoparticles' potential as a neurotherapeutic agent through combined AChE inhibition and antioxidative modulation. Despite these promising results, the study did not address pharmacokinetics, BBB permeability, or long-term biosafety, which remain crucial parameters for future translational validation of this bioengineered nanoplatform (46).

Theranostic applications

ZnO NPs integrate therapeutic and diagnostic functionalities, making them promising theranostic agents. Functionalization strategies improve aqueous stability, targeted delivery, and bioimaging efficiency, positioning ZnO QDs as multifunctional platforms suitable for monitoring therapeutic interventions in neurodegenerative disorders such as AD. Myco-fabricated ZnO-NPs exhibit antioxidant, anti-inflammatory, and AchE-inhibitory therapeutic effects and enable bioimaging via their fluorescence (28, 46-48). Sobhani *et al.* developed a multifunctional polyglycerol-modified zinc oxide quantum dot (ZnO-HPG QD) nanoplatform as a pH-sensitive fluorescent probe for targeted delivery of the anticancer drug doxorubicin (DOX). The synthesized QDs exhibited a uniform size of 6-8 nm, excellent water dispersibility, and high drug-loading efficiency (~82%). *In vitro* assays on MCF-7 breast cancer and HEK-293 normal cells demonstrated strong selective cytotoxicity toward malignant cells (IC_{50}≈35 μg/ml) and minimal toxicity to normal counterparts. Fluorescence microscopy confirmed cellular uptake and intracellular localization of the DOX-loaded QDs, while pH-dependent

release kinetics revealed rapid drug liberation under acidic tumor-like conditions (≈75% release at pH 5.5). These findings highlight the theranostic capability of ZnO-HPG QDs, integrating fluorescent imaging and targeted chemotherapy within a single nanoplatform. However, the absence of *in vivo* biodistribution and pharmacokinetic data limits immediate translational application (47).

Modified black phosphorus of QDs (BP QDs)

Black phosphorus nanosheets (BP NSs) or black phosphorus QDs (BP QDs) have emerged as highly versatile nanomaterials with significant biomedical potential, particularly in the context of neurodegenerative diseases such as PD (49). Their unique combination of tunable electronic structure, excellent optical properties, high charge carrier mobility, and intrinsic biocompatibility makes them attractive for a broad spectrum of biomedical applications, including bioimaging, biosensing, photodynamic therapy, and targeted clearance of pathogenic protein aggregates. Structurally, BP NSs possess surface functional groups (—OH, P—OH, P—O—P) indicative of partial oxidation, thereby enhancing their polarity and facilitating biological interactions (49). Despite these advantages, BP QDs are prone to degradation in aqueous or oxidative environments, compromising their structural integrity and functionality. Strategies such as PEGylation or surface coordination with titanium (IV) isobutoxide (TiL_4) have been employed to improve their stability and biological performance (49). Table 5 summarizes recent advances in the design and application of engineered BP QDs for diagnostic imaging, therapeutic intervention, and integrated theranostic strategies targeting neurological diseases.

Diagnostic applications

The tunable bandgap and distinctive photonic properties of BPQDs make them promising candidates for an advanced bioimaging and biosensing platform. Their high optical absorption, charge mobility, and strong near-infrared (NIR) response allow for sensitive detection of disease-related biomarkers and imaging of neuronal structures. BP-based nanomaterials efficiently penetrate the BBB, enabling *in vivo* visualization of their distribution, monitoring of therapeutic response, and tracking of protein aggregate clearance in neurodegenerative disease models (49, 51).

Yuwei Bu *et al.* reported a highly sensitive cathodic photoelectrochemical (PEC) aptasensor based on black phosphorus QDs (BPQDs) for detecting the amyloid β (Aβ) peptide, a key biomarker for AD. The BPQDs were synthesized via a modified Solvothermal method, where 18 mg of BP crystals were dispersed in N-methyl-2-pyrrolidone (NMP), combined with NaOH, and heated at 150 ˚C under nitrogen for 6 h. After two-step centrifugation, BPQDs with an average diameter of ~8 nm and high colloidal stability were obtained. Characterization by TEM, UV-Vis absorption, fluorescence spectroscopy, XPS, and Raman confirmed their nanoscale morphology, an optical band gap of 1.79 eV, and blue-green fluorescence (~530 nm), making them suitable as photoactive materials for PEC applications (50). For sensor fabrication, BPQDs were immobilized on ITO electrodes and functionalized with poly-L-lysine (PLL) to facilitate aptamer loading. Mechanistically, the Aβ-heme complex binds specifically to the aptamer, accelerating charge transfer and generating a signal-on cathodic photocurrent. Key experimental parameters were optimized: 1.0 mM aptamer and heme, 12 hr incubation, and -0.2 V bias potential. The PEC aptasensor exhibited a wide linear detection range from 1.0 fM to 100 nM, with a detection limit of 0.87 fM, high selectivity for the target biomarker, good stability over repeated cycles, and successful recovery (96.7-103.4%) in human serum samples. Limitations include the lack of *in vivo* validation and potential challenges in translating this PEC platform to clinical devices. Overall, this work demonstrates the potential of BPQDs as efficient photoactive materials for

Table 5. Provides a concise overview of recent research on engineered black phosphorus QDs (BP QDs) applied in diagnostic, therapeutic, and theranostic approaches for neurological disorders

		Targeted QDs	Disease	Experimental model	Results	Limitations	Ref
Applications	Diagnosis	Black phosphorus quantum dots (BPQDs) functionalized with PLL[a] and Aβ-specific aptamer	Alzheimer	*In vitro* (ITO electrode-based PEC sensor)[b], human serum samples	Detection limit: 0.87 fM; linear range: 1 fM-100 nM; high selectivity	No *in vivo* validation; clinical translation not demonstrated	(50)
	Therapeutic	Black Phosphorus QDs (BPQDs)	Parkinson	*In vitro*: PC12 neuronal cells with α-syn aggregation *In vivo*: MPTP-induced mice, hA53T α-syn transgenic mice	Disaggregation of α-syn fibrils Activation of autophagy Reduction of ROS[c] and mitochondrial dysfunction Rescue of neuronal viability and synaptic integrity Neuroprotection and behavioral improvement in mice	Need for detailed pharmacokinetics and biodistribution data - Translational relevance to humans uncertain Long-term safety and toxicity are unknown	(49)
		Lf-BP-Pae (Lactoferrin-functionalized Black Phosphorus Nanosheets loaded with Paeoniflorin)	Parkinson	*In vitro*: SH-SY5Y neuronal cells exposed to MPP^+ toxin *In vivo*: MPTP-induced PD mouse model	Enhanced BBB penetration via lactoferrin-mediated receptor transcytosis Strong NIR[d] absorption and photothermal stability allow controlled drug release Neuroprotection via antioxidative and anti-apoptotic mechanisms against MPP^+ toxicity Improved motor coordination, balance, and spontaneous locomotion in PD mice Minimal cytotoxicity, prolonged circulation, and high bioavailability confirmed	Long-term biosafety and biodegradation have not been assessed Dependence on NIR irradiation limits deep-brain application due to poor tissue penetration and potential heating	(51)
	Theragnostic	BP quantum-dots microbubbles (BPQDs@MBs) and BP nanosheet microbubbles (BPNSs@MBs), lipid/phospholipid-coated for stability	Parkinson	*In vitro*: 6-OHDA-induced PD neuronal/microglial cell models *In vivo*: PD rat model	Improved performance in rotarod and water-maze tests vs untreated PD rats BPQDs@MBs outperformed BPNSs@MBs in behavioral recovery Preservation of tyrosine hydroxylase-positive neurons (TH+) Reduced oxidative stress and microglial activation BPQDs promoted M2[e] anti-inflammatory polarization	Exact dosing (mg/kg), ultrasound acoustic parameters, and number of microbubbles not disclosed Off-target cavitation risk and translation to humans are not addressed	(52)

[a] poly-L-lysine (PLL), [b] ITO (Indium Tin Oxide)-based PEC (Photoelectrochemical) sensor, [c] reactive oxygen species (ROS), [d] Near inferred (NIR), [e] Anti-inflammatory M2 macrophages (M2)

highly sensitive, selective, and reproducible biosensing of neurodegenerative disease biomarkers (50).

Therapeutic strategies

Black phosphorus nanosheets (BPNSs) and their derivatives (e.g., BPNSs-PEG-Cy5) demonstrate potent therapeutic potential in PD models by targeting multiple pathogenic mechanisms. *In vitro*, BPNSs directly disassemble α-synuclein fibrils via hydrophobic interactions and β-sheet destabilization, activate autophagy pathways, reduce reactive oxygen species (ROS), preserve mitochondrial integrity, and maintain neuronal viability. They exhibit minimal cytotoxicity to PC12 and SH-SY5Y cells and achieve approximately 53% cellular uptake, with fibril disruption occurring within 24 hours. Autophagy activation is confirmed by increased LC3BII/LC3BI ratios, autophagosome formation, and up-regulation of autophagy-related genes (Atg7, Atg16l2); inhibition with chloroquine or 3-methyladenine abolishes these effects, validating the mechanistic role of autophagy (49).

In vivo, BPNSs and BPNSs-PEG-Cy5 cross the blood-brain barrier, accumulate in the brain, and significantly reduce α-synuclein aggregation while protecting tyrosine hydroxylase-positive dopaminergic neurons in both hA53T transgenic and MPTP-induced mouse models. Similar neuroprotective effects are observed in C. elegans models, where BP nanomaterials extend lifespan, preserve neuronal integrity, reduce oxidative stress, and enhance autophagy. Stabilized BPQDs also promote α-syn degradation and alleviate PD-like symptoms, highlighting the broad therapeutic relevance of BP-based nanomaterials. Despite these promising results, exact dosing parameters remain unspecified, long-term safety and toxicity have yet to be evaluated, and translational applicability to human PD requires further investigation. Overall, BPNSs represent a multi-modal nanotherapeutic platform that concurrently addresses protein aggregation, oxidative stress, mitochondrial dysfunction, and neuronal loss, offering a compelling strategy for PD intervention (49).

In the 2020 study, a brain-targeted nanotherapeutic system was engineered using lactoferrin-functionalized black phosphorus nanosheets (Lf-BP) loaded with paeoniflorin (Pae) to overcome the blood–brain barrier (BBB) and enhance PD therapy. Functionalized BPNSs, particularly Lf-BP-Pae, exhibited superior stability, dispersibility, and drug-loading capacity, addressing key limitations of pristine BP. The lactoferrin coating enabled receptor-mediated transcytosis across the BBB, increasing brain accumulation without compromising barrier integrity or inducing hemolysis. Moreover, BP's intrinsic near-infrared (NIR) absorption and the high photothermal stability of Lf-BP-Pae facilitated controlled drug release under NIR irradiation, thereby enhancing spatial and temporal precision in drug delivery (51). *In vitro,* Lf-BP-Pae exhibited minimal cytotoxicity at concentrations ranging from 5 to 40 μg/mL and potent neuroprotective activity in SH-SY5Y neuronal cells exposed to MPP^+-induced oxidative toxicity, thereby improving cellular viability and dopaminergic function. *In vivo*, following intravenous administration at 2 mg/kg (repeated dosing over 14 days), both Lf-BP-Pae and its PEGylated derivative successfully crossed the BBB, accumulated within the brain parenchyma, and significantly reduced dopaminergic neuron loss while improving motor coordination, balance, and spontaneous locomotion in MPTP-induced PD mice. The system effectively integrates drug delivery, photothermal responsiveness, and neuroprotective efficacy, representing a multifaceted nanoplatform for targeted PD therapy. However, despite these advances, several limitations remain: precise pharmacokinetic characterization, long-term biosafety assessment, and biodegradation profiling were not comprehensively reported. The dependence on NIR-assisted activation may also constrain clinical translation due to limited light penetration and potential thermal safety concerns in deep brain tissues. Nevertheless, this study provides robust proof-of-concept evidence that functionalized BP nanosheets can serve as a versatile, BBB-permeable nanotherapeutic vehicle, capable of ensuring controlled drug release and achieving significant neuroprotective outcomes in PD models (51).

Theraneustic applications

BP nanomaterials exemplify the concept of theranostics, offering integrated diagnostic and therapeutic functionality in neurodegenerative disease management. Dual-mode action of BPNSs simultaneously enables α-synuclein clearance (therapeutic) and real-time imaging of neuronal processes (diagnostic)(49). Photothermal-triggered release of BP, owing to its strong NIR absorption, enables on-demand drug release while enabling concurrent thermal imaging and therapy (51). Neuroprotection and imaging synergy of In PD models, BPQDs@MBs and BPNSs@MBs improve learning, memory, and motor functions while facilitating non-invasive imaging of disease progression (51, 52). Toxicity remains dose-dependent and transient, with full recovery observed after several days, supporting their suitability for clinical translation (52).

In a 2024 report, Guo *et al.* describe an innovative theranostic strategy pairing black phosphorus microbubbles (BPQDs@MBs and BPNSs@MBs) with focused ultrasound (FUS) to transiently open the blood–brain barrier and deliver BP-based nanomaterials into PD models. The authors demonstrate that repeated intravenous administration of BP-microbubbles combined with focal ultrasound (1.5 min exposure to the right hemisphere every 3 days over a two-week course) enables brain entry of both BP QDs and nanosheets, elicits antioxidant and anti-apoptotic effects, promotes an anti-inflammatory (M2) microglial phenotype (notably with BPQDs), and produces meaningful improvements in behavioral assays (water-maze and rotarod) while preserving tyrosine hydroxylase-positive neurons. These findings highlight an attractive dual mechanism, physical BBB modulation by ultrasound plus intrinsic BP bioactivity, that can augment neuroprotection in PD models. For translational progression, the field requires full disclosure of dose metrics, systematic dosimetry studies, comprehensive biodistribution/pharmacokinetics, and larger-animal safety studies to evaluate the risk of ultrasound-induced off-target cavitation and the long-term fate of BP materials in the CNS (52).

Another QDs: Perovskite QDs (PQDs), cadmium selenide QDs (CdSe QDs), and molybdenum disulfide QDs (MoS2 QDs)

PQDs, particularly lead halide variants, and cadmium selenide (CdSe) QDs represent two prominent classes

of semiconductor nanocrystals with exceptional photoluminescent properties, making them highly attractive for bioimaging and theranostic applications. PQDs generally adopt a cubic crystalline structure (~20 nm) with high photoluminescence quantum yields, narrow and tunable emission, and efficient light emission, enabling applications in X-ray imaging, fluorescence, MRI, and optoelectronic devices, including displays, lasers, and solar cells (53, 54). However, their direct biomedical use is limited by poor stability in aqueous media and potential cytotoxicity from released halide and cesium ions. To overcome these challenges, various surface-engineering strategies have been developed, including polymer coatings, antibody functionalization, and encapsulation within amphiphilic micelles or block copolymers, thereby improving colloidal stability and biocompatibility (54, 55). CdSe QDs, often consisting of a Cd/Se core coated with a ZnS shell, exhibit high photostability, size-tunable emission, and large Stokes shifts, with broad absorption and narrow emission spectra enabling multiplexed imaging in complex tissues both *in vitro* and *in vivo* (53, 55). Beyond imaging, CdSe QDs serve as theranostic platforms, enabling controlled delivery of therapeutic agents, including gene-editing tools, while their intrinsic fluorescence enables real-time monitoring of cellular uptake. Surface modification enhances biocompatibility and mitigates cytotoxicity, although long-term cadmium toxicity remains a consideration (53-55). Compared with carbon- or graphene-based QDs, both PQDs and CdSe QDs offer superior optical performance, tunable emission, and versatile surface functionalization, highlighting their potential as engineered nano-ceramic QDs for integrated diagnostic, therapeutic, and biomedical applications. Table 6 highlights recent advances in engineered PQDs, CdSe QDs, and MoS_2 QDs for diagnosis, therapy, and theranostic applications in neurological diseases.

Diagnostic applications

Perovskite QDs exhibit high photoluminescence quantum yields, narrow emission bands, and strong light-emitting efficiency, making them ideal for fluorescence-based imaging and optoelectronic applications. Surface modifications, such as PEG-PCL coatings or polymer/antibody encapsulation, improve colloidal stability and biocompatibility, overcoming their intrinsic sensitivity to aqueous environments and ion-induced cytotoxicity (55). PEG-PCL-coated PQDs are FDA-approved for biocompatibility and have been successfully used as biological probes. For example, they enable *in vivo* quantification of hydrogen sulfide (H_2S), a key gaseous signaling molecule, in living cells and zebrafish models (55). Compared with hydrophobic molecule functionalization, non-PEG polymer coatings, or glass embedding, PEG-PCL encapsulation minimizes adverse effects on nanoscale size, colloidal stability, and photoluminescence, ensuring reliable diagnostic performance (53). Amphiphilic PEG-PCL coating of PQDs simultaneously addresses diagnostic and potential therapeutic challenges. The micelle's hydrophobic core protects the PQD surface, while hydrophilic PEG chains maintain dispersibility in aqueous environments and minimize ion release, reducing cytotoxicity (55). By preserving optical properties and particle size, PEG-PCL-coated PQDs can serve as both fluorescent imaging agents and potential carriers for therapeutic molecules, opening avenues for theranostic applications (53, 55). PEG-PCL encapsulation retains over 94% of the initial photoluminescence quantum yield after 15 days of immersion, demonstrating durability for longitudinal biomedical studies (55). Collectively, these features position PEG-PCL-coated PQDs as versatile platforms for theranostic applications, integrating imaging capability with a safer biological profile.

In the 2022 study, water-dispersible $CsPbBr_3$ perovskite nanocrystals (NCs) were developed for super-resolution single-molecule localization microscopy (SMLM),

Table 6. Provides a concise overview of recent research on engineered perovskite QDs (PQDs), cadmium selenide(CdSe QDs), and MoS2 QDs applied in diagnostic and therapeutic approaches for neurological and general disorders

		Targeted QDs	Disease	Experimental model	Results	Limitations	Ref
Applications	Diagnosis	PEG–PCL-encapsulated perovskite QDs	H_2S[a] monitoring	Cells *(in vitro)*, zebrafish *(in vivo)*	High water-resistance, biocompatible, stable fluorescence, long-term H_2S tracking	Dose not specified, no mammalian model or BBB study, potential Pb toxicity, limited biodistribution data	(55)
		$CsPbBr_3$[b] perovskite nanocrystals (NCs) modified for water dispersion	General bioimaging study	*In vitro* (cellular imaging), targeted fluorescent labeling of HeLa and NIH-3T3[c] cells	Achieved localization accuracy of ~10 nm, enabling super-resolution bioimaging. Excellent photostability and fluorescence intensity in aqueous conditions Maintained low cytotoxicity and biocompatibility Stable dispersion in biological buffers for extended imaging	No *in vivo* imaging validation Long-term toxicity and biodegradation have not been evaluated Lead-based composition (Pb^{2+}) poses biocompatibility concerns for clinical use	(48)
		CdSe[d]/CdS[e]/ZnS[f] QDs with aptamers	Alzheimer's biomarkers (AβO, tau)[g]	Human serum (*ex vivo*)	Ultra-sensitive detection; high precision; good recovery	Diagnostic only; no *in vivo*/BBB data; cytotoxicity not assessed	(56)
		NGR[h] peptide-modified PEGylated CdSe/ZnS QDs	Glioma	Cell lines: C6 glioma; Animal: Sprague-Dawley rats with intracerebral C6 tumors	Crossed BBB, selectively accumulated in glioma and tumor vasculature; strong fluorescence labeling at 2 nM (*in vitro*) and 1 nmol (*in vivo*)	Diagnostic only; long-term safety, biodistribution, and peptide density optimization not fully assessed	(57)
	Therapeutic	CdSe QDs conjugated with Cas9	Microglial genome editing (CRISPR-Cas9 delivery)	Microglial cells *in vitro*	Low cytotoxicity; modulates pro-/anti-inflammatory cytokines; controlled Cas9 release	Limited editing efficiency; instability and aggregation of complexes; further optimization needed	(58)
		CdSe/ZnS QDs conjugated with MOG peptide	Multiple Sclerosis	Murine *EAE* model	Induced antigen-specific immune tolerance; promoted T_REG expansion; reduced Th1 responses; delayed disease onset; decreased demyelination, neuronal apoptosis, and axonal damage	Preclinical model only; challenges in scaling peptide-QD conjugates for clinical use; long-term safety and biodistribution not fully assessed	(59)
		Ultrasmall MoS_2 QDs	Alzheimer	*In vitro*: SH-SY5Y human neuroblastoma cells exposed to $A\beta_{1-42}$ oligomers (20 μM); *In silico*: Discrete Molecular Dynamics simulation	Inhibited Aβ fibrillation Restored membrane fluidity Improved cell viability	Only *in vitro* + simulations High QD: Aβ ratios required No *in vivo*, pharmacokinetics, or long-term toxicity data	(60)

[a] Hydrogen sulfide (H_2S), [b] Cesium Lead Bromide ($CsPbBr_3$), [c] Cadmium selenide (CdSe), [d] Cadmium sulfide (CdS), [e] Zinc sulfide (ZnS), [f] a fibroblast cell line (NIH-3T3), [g] Amyloid-beta oligomers (AβO), a microtubule-associated protein (tau), [h] Aminopeptidase N (NGR)

achieving remarkable diagnostic precision at the nanoscale. These NCs, with an average diameter of 10-12 nm, were functionalized to ensure aqueous stability and biocompatibility, addressing the solubility limitations of conventional perovskite QDs. When applied to *in vitro* imaging of HeLa and NIH-3T3 cells at concentrations between 10-50 μg/ml, the NCs exhibited high fluorescence intensity, superior photostability, and localization accuracy of approximately 10 nm, enabling highly resolved and targeted bioimaging. The study demonstrates the strong potential of $CsPbBr_3$ nanocrystals as next-generation fluorescent probes for cellular diagnostics. Nevertheless, challenges, including lead toxicity, lack of *in vivo* validation, and unclear biodegradation profiles, limit their immediate translational applicability for clinical imaging (48). In this study, dual-color-engineered CdSe/CdS/ZnS core/shell/shell QDs served as the targeted QDs, functionalized with aptamers for the simultaneous detection of two hallmark biomarkers of AD, namely amyloid-β oligomers (AβO) and tau protein. The experimental model comprised water-soluble QDs in an aptamer-quencher assembly (QDs-DNA/Au nanorods@polydopamine) and clinical human serum samples. The sensor achieved ultra-high sensitivity, with detection limits of ~50 pM for AβO and ~20 pM for tau, high precision (RSD < 5 %), and excellent recovery (95-104 %) in serum. These results demonstrate the feasibility of a multiplexed diagnostic platform for AD core biomarkers. However, the limitations include that this is purely a diagnostic/imaging platform (rather than therapeutic), that it remains *ex vivo*/serum-based (with no *in vivo* CNS model or BBB penetration), and that potential issues of cytotoxicity or long-term biocompatibility of CdSe-based QDs remain unaddressed (56).

Also, in 2017, a targeted diagnostic nanoplatform based on NGR peptide–modified PEGylated CdSe/ZnS QDs (QD-NGR) was introduced for selective fluorescence imaging of glioma and tumor vasculature. By exploiting the NGR peptide's affinity for CD13, which is overexpressed on glioma endothelial cells, the engineered QDs exhibited efficient blood–brain barrier (BBB) penetration and preferential accumulation in C6 glioma cells and intracerebral tumors in Sprague-Dawley rats. *In vitro* imaging at 2 nM and *in vivo* imaging after 1 nmol intravenous administration produced strong fluorescence signals, confirming both targeting specificity and imaging sensitivity (57). While the platform demonstrated high diagnostic efficiency, it remained purely imaging-oriented, lacking therapeutic functionality. Limitations include the absence of long-term biodistribution and toxicity evaluations, as well as the lack of optimization of targeting ligand density. Overall, this study establishes QD-NGR as a promising targeted nanodiagnostic tool for real-time glioma visualization, with future potential for theranostic adaptation.

Therapeutic strategies

The CRISPR-Cas9 system represents a precise and adaptive genome-editing tool. CdSe QDs have recently been explored as delivery vectors for Cas9 into microglial cells. Experimental studies demonstrated that CdSe QDs exert minimal effects on cell viability or baseline microglial functions. At higher concentrations (5 nM), CdSe QDs reduced pro-inflammatory mediators (NO, IL-6, IL-1β) while promoting anti-inflammatory cytokines (IL-23, BDNF, IL-4, IL-13, IL-25). Cas9/QD conjugates are primarily internalized via clathrin-mediated endocytosis, and inhibition of this pathway markedly reduces cellular uptake. Surface conjugation of Cas9 allows gradual disassembly under reducing intracellular conditions, enabling controlled Cas9 release into the cytosol and nucleus over 24-72 hours (58). Despite their potential, overall gene-editing efficiency remains limited. Attempts to enhance performance, including replacing biotin–streptavidin linkages with histidine–zinc interactions or introducing a Cys80-to-Ser mutation in Cas9, did not substantially improve editing outcomes. Instability of maleimide–thiol bonds and irregular aggregation of Cas9/QD complexes hinder efficient nuclear entry. Therefore, further optimization of conjugation strategies and stabilization methods is essential for *in vivo* and clinical applications (58).

Therefore, engineered CdSe QDs have demonstrated some theranostic potential, particularly in diagnostic and imaging applications; their therapeutic efficacy in neurodegenerative diseases remains insufficiently explored. For perovskite QDs (PQDs), no studies to date have reported combined therapeutic and diagnostic (theranostic) applications in neurodegenerative contexts. Current research on PQDs is largely limited to biosensing, imaging, or biomarker detection. Critical challenges, including blood–brain barrier (BBB) penetration, long-term biocompatibility, clearance, and potential lead toxicity, remain major obstacles. Consequently, the development of lead-ceramic QDs for theranostic purposes in neurodegenerative diseases represents a significant research gap, highlighting the need for systematic investigations into safe and effective therapeutic strategies.

In another work, Hess *et al.* developed a targeted immunotherapeutic platform using CdSe/ZnS QDs (QDs) conjugated with self-antigen peptides (MOG) to induce antigen-specific immune tolerance in a murine model of multiple sclerosis (experimental autoimmune encephalomyelitis, EAE). By precisely tuning the density of MOG peptides on the QD surface, the study demonstrated that lower-density QDs administered in higher numbers were most effective in promoting regulatory T cell (T-REG) expansion while minimizing pathogenic Th1 responses, leading to delayed disease onset, reduced clinical scores, and decreased demyelination, neuronal apoptosis, and axonal damage. The QDs efficiently localized to draining lymph nodes and interacted with antigen-presenting cells to modulate immune responses without eliciting broad immunosuppression. The fluorescent properties of QDs also enabled direct visualization of biodistribution and immune engagement. Limitations include the preclinical nature of the model, potential challenges in scaling peptide-QD conjugates for clinical use, and incomplete long-term safety assessment. Overall, this study highlights a precision nanotherapeutic strategy in which QDs serve as a tunable platform to orchestrate targeted immune tolerance, with promising implications for the treatment of autoimmune disorders (59).

MoS_2 QDs (MoS_2 QDs) are ultrasmall nanostructures, typically 2-6 nm in size, derived from the 2D layered transition-metal dichalcogenide molybdenum disulfide. They possess abundant edge sites and surface defects, enabling strong interactions with biomolecules, size-tunable photoluminescence (blue-green emission), and

good short-term biocompatibility in cellular models. Due to their unique physicochemical properties, MoS_2 QDs are widely explored for bioimaging, biosensing, drug delivery, and therapeutic applications, including inhibition of amyloid-beta aggregation in AD (26). Ultrasmall MoS_2 QDs (MoS_2 QDs), with diameters of 2-6 nm, have demonstrated significant potential for mitigating amyloid-beta (Aβ) toxicity in AD. In Tang *et al.* (2021), SH-SY5Y human neuroblastoma cells were treated with $Aβ_{1-42}$ oligomers (20 μM) in the presence of MoS_2 QDs at 10 and 100 μM. The study employed Thioflavin-T (ThT) fluorescence assays to quantitatively assess Aβ fibrillation, Laurdan generalized polarization (GP) imaging to measure membrane fluidity, and cell viability assays (Trypan Blue and PI staining) to evaluate cytotoxicity. MoS_2 QDs effectively reduced ThT fluorescence by up to ~60-70% at the higher dose, indicating strong inhibition of fibril formation. Concurrently, Laurdan GP analysis revealed that QDs restored membrane fluidity close to control levels, reversing the stiffening effect induced by Aβ oligomers. Cell viability was significantly improved, with survival rates increasing from ~55% in Aβ-treated cells to ~85% in the presence of 100 μM QDs. Mechanistically, the ultrasmall QDs provide abundant surface-edge sites that "cage" aggregation-prone regions of Aβ, thereby limiting β-sheet propagation and oligomer expansion. These results quantitatively support the role of MoS_2 QDs as multifunctional nanotherapeutics that directly counter Aβ-induced membrane disruption and cytotoxicity in neuronal cells (60).

Other strategies using targeted QDs in neurodegenerative disease

Recently, there has been a growing focus on disease-modifying therapeutic strategies that address the underlying molecular drivers, rather than treating symptoms alone. Table 7 summarizes the key features and performance of the other strategies using the quantum dot platform for neurodegenerative disease research, including QD type, target, experimental model, mechanism, size, detection range, outcomes, and limitations.

Lin *et al.* developed an imaging platform using inorganic CdSe/ZnS core-shell QDs (QD605) functionalized with amino-PEG at 30 nM to perform real-time 3D visualization of amyloid aggregates, including $Aβ_{1-42}$, tau, and α-synuclein, *in vitro*. Experiments conducted with SH-SY5Y human neuroblastoma cells and complementary fluorescence, confocal, and TEM imaging allowed quantitative assessment of aggregation kinetics and fibril morphology. Using a microliter-scale high-throughput screening (MSHTS) system, the authors evaluated the inhibitory effects of compounds such as rosmarinic acid, reporting EC_{50} values of 20.6 μM for Aβ and 2.1 μM for α-synuclein. Mechanistically, the QDs acted via non-specific surface binding, enabling sensitive detection of fibril growth without interfering with the aggregation process itself. Key outcomes included successful 3D reconstruction of aggregation patterns and quantitative monitoring of fibril dynamics, demonstrating the platform's utility for high-resolution analysis. However, the study was limited to *in vitro* and computational models, with no *in vivo* validation, long-term cytotoxicity

Table 7. Other features and performance of the quantum dot platform for neurodegenerative disease research

QD Types	Disease Target	Experimental Model	Mechanism of Action (Non-Targeted)	Dose / Size	Outcomes	Limitations	Ref
Graphene QDs (MABM-GQDs)[a]	PD[b]	Neuro-2a, SH-SY5Y cells; C57BL/6 mice	Anti-aggregation via π–π stacking, hydrogen bonding; defibrillation of α-syn	50-200 μg/ml; 5 mg/kg; 5-8 nm	78% inhibition of α-syn aggregation; neuron protection; motor recovery	limited imaging; incomplete pharmacokinetics	(9)
Fucoidan-derived Carbon Dots (FDCDs)	PD	MPP⁺-induced PC12 cells; Mouse	ROS scavenging, mitochondrial stabilization, anti-inflammatory, spontaneous BBB penetration	25-100 μg/ml (*in vitro*); 5 mg/kg (*in vivo*); 5-8 nm	BBB crossing; dopaminergic neuron rescue; improved motor function	incomplete pharmacokinetics and long-term toxicity	(23)
Photomodulatable Carbon Dots (PCDs)	AD[c]	SH-SY5Y, PC12 cells; C. elegans CL2006	Light-triggered $^1O_2$ generation; photo-controlled fibril disruption; spatiotemporal therapy	50-100 μg/ml; 3-6 nm	Light-controlled Aβ disaggregation; behavioral recovery in worms	No mammalian *in vivo* validation; weak BBB penetration; light penetration limits	(36)
Graphene QDs	PD	Primary neurons; murine PD model	Direct inhibition of α-syn fibrillization; antioxidant & mitochondrial protection	Not specified (~ <10 nm)	BBB penetration, reduced α-syn toxicity, motor improvement	No long-term biodistribution; lack of delivery optimization	(44)
Nitrogen-doped carbonized polymer dots (N-CPDs) with high fluorescence and biocompatibility	AD	*In vitro*: Aβ monomers/fibrils; *In vivo*: transgenic C. elegans CL2006	Inhibits fibrillization and disaggregates fibrils via electrostatic, hydrogen-bonding, and hydrophobic interactions; fluorescence enables imaging	100 μg/~5 nm	Reduced Aβ[d] aggregation. Plaque imaging via fluorescence. Plaque clearance and lifespan extension in C. elegans	Limited to C. elegans; BBB permeability and long-term toxicity not assessed; scalability untested	(61)
Enzyme-formed CdS quantum dots generated by ALP[f]	AD	*In vitro* biosensor platform *(no in vivo* disease model*)*.	ALP-conjugated antibody binds BDNF[e] → enzymatic reaction produces CdS QDs → LSPR from Au@SiO_2 enhances fluorescence → signal ∝ BDNF concentration.	Size of CdS QDs ~4.056 nm	Very high sensitivity for BDNF detection; strong linear correlation (R^2 ≈ 0.938) between fluorescence signal and BDNF concentration	Not tested in biological fluids / patients; potential toxicity of CdS QDs; stability and specificity in complex media unknown	(62)
CdSe/ZnS QD605 (amino-PEG modified)	AD, PD (Aβ, Tau, α-Syn aggregation research imaging)	SH-SY5Y cells, MSHTS[g] system	Surface adsorption-based real-time monitoring of amyloid aggregation (non-interactive)	30 nM	High-resolution 3D fibril visualization; quantification of aggregation kinetics	*In vitro* only; not therapeutic; no BBB study or toxicity data	(63)
CdSe/ZnS QDs (JB577 peptide)	Brain development (non-therapeutic, non-targeted delivery)	In ovo chick embryo	Size-based and peptide-mediated cellular penetration; developmental tracing	~9.5 nm	Widespread neuronal distribution; low acute neurotoxicity	Limited to developmental studies; not disease-specific; no targeting	(64)
CdSe/ZnS QDs phagocytosed by macrophages	Glioma imaging (non-biological targeting)	Rodent tumor model	Immune cell–mediated "Trojan-horse" tumor localization (non-receptor targeting)	~15-20 nm	Macrophage-mediated QD accumulation in gliomas: clear tumor imaging	Toxic cadmium core; no therapeutic function; no BBB penetration	(65)
CdSe/ZnS core-shell embedded in liposomes.	PD	*In vitro*: bEnd.3 brain endothelial cells; *In vivo*: nude mice for bioimaging and biodistribution	Energy-dependent endocytosis via clathrin- and caveola-mediated pathways; passive targeting to brain via liposome-mediated transport	Liposome size ~140 nm; QD and drug dose optimized for cellular uptake and *in vivo* imaging.	Enhanced BBB[h] penetration. Reduced systemic distribution (liver, heart). Real-time fluorescence imaging of brain accumulation Improved delivery of apomorphine to brain	Short-term imaging study; long-term toxicity unassessed Controlled drug release is not fully characterized Scalability and translation to humans are uncertain	(66)
CdSe/CdS/ZnS core/interlayer/shell QDs, PEGylated	Deep-brain imaging	*In vivo*: mice (open-skull and intact-skull); 3PF microscopy	Passive tissue penetration; enhanced 3-photon absorption via band gap engineering; ZnS shell passivates defects	~15–40 nm	High-resolution imaging (capillaries ~0.8 μm); depth up to 1550 μm; high quantum yield	potential cadmium toxicity; long-term biodistribution not assessed; translation to humans untested	(67)

[a] Methyl N-allyl N-benzoylmethioninate - Graphene Quantum Dots (MABM-GQDs), [b] Parkinson's disease (PD), [c] Alzheimer's disease (AD), [d] Amyloid β (Aβ), [e] Brain-derived neurotrophic factor (BDNF), [f] Alkaline phosphatase (ALP), [g] Microliter-scale high-throughput screening (MSHTS), [h] Blood–brain barrier (BBB)

assessment, or evaluation of physiological relevance, indicating that the platform serves primarily as a research tool for aggregation analysis rather than a therapeutic or targeted intervention (63). In a recent study, a nanoplatform based on fucoidan-derived carbon dots (FDCDs) for BBB penetration and neuroprotective treatment of PD was reported. The FDCDs, synthesized through a one-step hydrothermal carbonization of the marine polysaccharide fucoidan, exhibited a uniform spherical morphology with an average diameter of 5-8 nm and a strong negative surface charge attributed to abundant -SO_4^{2-} and -OH functional groups. These surface moieties not only conferred high colloidal stability and biocompatibility but also facilitated electrostatic and receptor-mediated transcytosis across the BBB (23). *In vitro* experiments using MPP^+-induced PC12 neuronal cells, treatment with 25-100 µg/ml of FDCDs resulted in a significant reduction of reactive oxygen species (ROS) levels, restoration of mitochondrial membrane potential, and suppression of apoptotic signaling. Furthermore, *in vivo* administration of MPTP-induced PD mice (5 mg/kg, intravenous) demonstrated efficient BBB traversal and targeted accumulation in the midbrain, where FDCDs rescued dopaminergic neurons in the substantia nigra and improved locomotor performance on the rotarod and pole tests. Mechanistically, the sulfated surface groups of FDCDs enhanced neuronal uptake and activated antioxidant defense pathways, reducing oxidative stress and neuroinflammation, while maintaining excellent biosafety with no detectable hepatic or renal toxicity (23). Overall, this study highlights naturally derived FDCDs as promising BBB-penetrant nanotherapeutics that combine antioxidant, anti-inflammatory, and neuroprotective properties for PD management. However, limitations include the lack of long-term toxicity studies, unclear mechanisms of BBB translocation, and the absence of receptor-mediated targeting, suggesting that while FDCDs are promising neuroprotective nanocarriers, further investigations are required to optimize their therapeutic efficacy and translational potential.

In this context, carbon and graphene QDs have emerged as promising early-stage therapeutic agents due to their intrinsic affinity for misfolded proteins, antioxidant capacity, and anti-inflammatory properties, despite lacking ligand-mediated targeting mechanisms. The surface-enriched functional groups (-COOH, -OH, -NH_2) and π-conjugated structures enable spontaneous interactions with Aβ, tau, and α-synuclein aggregates via π–π stacking, hydrogen bonding, and electrostatic forces, leading to inhibition of nucleation, fibril destabilization, and suppression of synaptic toxicity (36). Moreover, these QDs exhibit ROS scavenging, mitochondrial protection, and redox-regulating capabilities, making them particularly suitable for MS therapeutics, where oxidative stress and immune dysregulation drive demyelination and neuronal apoptosis (10).

Beyond conventional diagnostic applications, QDs have evolved as multifunctional platforms for therapeutic intervention in neurodegenerative disorders. Among these, photomodulatable carbon dots (PCDs) represent a promising non-targeted therapeutic approach that uses spatiotemporal light activation rather than biological targeting to regulate pathogenic protein aggregation. In this context, Chung *et al.* engineered photoresponsive carbon dots (PCDs, 3-6 nm) via a solvothermal synthesis using citric acid and phenylenediamine. The amine- and carbonyl-rich surface enabled efficient $^1O_2$ generation under visible light (450-470 nm), leading to the selective disruption of β-sheet-rich $A\beta_{1-42}$ fibrils and their conversion into non-toxic, amorphous species. *In vitro* experiments in SH-SY5Y and PC12 neuronal cells demonstrated significant attenuation of Aβ-induced cytotoxicity, maintaining cell viability at ~85% when treated with 50-100 µg/ml PCDs under controlled light exposure. *In vivo* validation using the C. elegans CL2006 transgenic AD model confirmed reduced Aβ deposition, suppressed progression of paralysis, and behavioral improvement when PCDs (100-200 µg/mL) were activated by localized light irradiation. Critically, this strategy enables spatiotemporal precision, limiting off-target effects by activating anti-aggregation mechanisms only at designated sites and timepoints.

However, therapeutic translation remains constrained by limited tissue penetration of visible light, the absence of BBB-targeting capabilities, and the lack of *in vivo* validation in mammals. Although the intrinsic fluorescence of PCDs offers imaging potential, their role remains predominantly therapeutic rather than fully theranostic. Collectively, the study underscores the potential of light-activated, non-biologically targeted CQDs as functional nanoagents for Aβ inhibition with high spatial control, while highlighting the need for NIR-responsive designs and brain-targeted modifications to advance clinical feasibility (36).

Nitrogen-doped carbonized polymer dots (N-CPDs) have been demonstrated as a multifunctional nanoplatform with significant potential for targeting AD pathology, as they act simultaneously as potent scavengers of β-amyloid (Aβ) aggregates and as fluorescent probes for their detection. Nitrogen doping enhances electrostatic, hydrogen-bonding, and hydrophobic interactions with Aβ species, enabling both inhibition of fibrillization and disaggregation of preformed plaques *in vitro*. Importantly, *in vivo* studies using the transgenic C. elegans model (CL2006) showed effective plaque clearance and an extension of organismal lifespan, highlighting the translational potential of this approach (61). This study exemplifies the design of theranostic nanomaterials that combine diagnostic and therapeutic functionalities within a single construct, leveraging the inherent biocompatibility, photostability, and tunable surface chemistry of polymer-derived carbon dots. Despite promising outcomes, limitations such as a lack of data on blood-brain barrier permeability, long-term biocompatibility in mammalian models, and scalability of synthesis underscore the need for further preclinical validation. Overall, Gao *et al.* provide a compelling framework for developing multifunctional carbon-based nanodots for neurodegenerative disease applications, aligning with current trends in precision nanomedicine (61).

One of the most promising approaches involves the application of nanotechnology-based therapeutics, particularly GQDs, which have demonstrated potent anti-aggregation effects in preclinical models. In a 2023 study, a non-biologically targeted yet functionally engineered graphene quantum dot nanocomposite (MABM-GQDs) was developed to disassemble pathogenic α-synuclein fibrils associated with PD. The nanosystem, with a particle size of 5-8 nm and rich in π-conjugated, carboxyl, and amine surface groups, engaged in π–π stacking, hydrogen

bonding, and hydrophobic interactions with the N-terminal region of α-syn, promoting defibrillation and preventing further fibril propagation. *In vitro* experiments using Neuro-2a and SH-SY5Y neuronal cells demonstrated a 30-50% reduction in cytotoxicity at 50-200 μg/ml, with >85% cell viability. Notably, the nanocomposite achieved up to 78% inhibition of α-syn aggregation, outperforming non-conjugated counterparts. *In vivo*, repeated intraperitoneal administration (5 mg/kg) in C57BL/6 PD mice improved cerebral blood flow, enhanced dopaminergic neuronal survival (↑TH+ expression), and restored motor function. Although primarily therapeutic, the intrinsic fluorescence enabled limited imaging-based monitoring, suggesting emerging theranostic potential. However, the absence of BBB-targeting ligands, limited pharmacokinetic data, and lack of long-term toxicity assessment restrict immediate translational applicability (9). Overall, MABM-GQDs represent a transitional platform that bridges non-targeted therapeutic GQDs and more advanced, functionalized, targeted GQD nanocarriers. According to the study, Yu et al. developed an ultra-sensitive *in vitro* nanoplatform for detecting brain-derived neurotrophic factor (BDNF), employing enzyme-formed CdS QDs (QDs) in combination with silica-coated gold nanoparticles (Au@SiO_2). In this system, alkaline phosphatase (ALP) conjugated to a secondary BDNF antibody catalyzes the formation of CdS QDs upon substrate interaction, producing a fluorescence signal that is further enhanced by local surface plasmon resonance (LSPR) from the gold nanoparticles (62). The thickness of the silica shell is precisely controlled to optimize the QD-Au spacing, thereby maximizing signal amplification. Notably, the QDs are non-targeted, generated in situ within the assay rather than delivered to specific cells or tissues, and the platform operates entirely *in vitro*. The QDs are small (~4 nm) and enable the detection of BDNF at ultra-low concentrations, exhibiting a strong linear correlation between fluorescence intensity and analyte concentration. Although the system demonstrates high sensitivity and selectivity for BDNF detection, limitations include the absence of testing in biological fluids or patient samples, potential cytotoxicity of CdS QDs, and unverified stability in complex physiological environments. Overall, this study exemplifies a diagnostic, non-targeted quantum dot platform capable of precise biomarker quantification for applications in neurodegenerative disease research (62).

While these nanomaterials are not biologically targeted, their surface chemistry, driven by multifunctional actions, enables them to modulate key pathogenic pathways during the prodromal phase of AD, PD, and MS. Although conventional therapies can slow disease progression, they do not reverse demyelination or prevent long-term neurodegeneration. Recent advances focus on immune modulation, neuroprotection, and targeted nanotherapeutics as more effective disease-modifying strategies.

Kim *et al.* (2018) demonstrated that GQDs can act as a therapeutic nanoplatform to prevent α-synuclein aggregation in PD models. The GQDs, synthesized as small fluorescent graphene nanoparticles, were shown to inhibit fibrillization and disassemble preformed α-synuclein fibrils via a combination of electrostatic and hydrophobic interactions, thereby reducing β-sheet content (44). In neuronal cultures, GQDs protected dopaminergic neurons from α-synuclein preformed fibril-induced toxicity, preserved synaptic proteins (SNAP25, VAMP2), and maintained mitochondrial function. In *in vivo* murine PD models, systemic administration of GQDs resulted in crossing of the blood-brain barrier, decreased α-synuclein pathology, reduced dopaminergic neuron loss, and improved motor behavior. The study highlights GQDs as a partially targeted, neuroprotective nanotherapeutic that combines anti-aggregation activity with functional neuronal preservation (44). Limitations include incomplete characterization of long-term biodistribution, clearance, and potential chronic toxicity, as well as the need for further optimization of dosing and delivery strategies to facilitate clinical translation. Overall, this work provides compelling evidence that GQDs represent a promising theranostic approach for PD, addressing both pathological aggregation and neuronal dysfunction.

In addition to Thioflavin-T fluorescence assays, molecular dynamics simulations, and neuronal culture models, GQDs have been shown to significantly reduce α-synuclein toxicity, preserve dopaminergic neurons, decrease Lewy body-like inclusions, and improve mitochondrial function. Agarwal *et al.* (2015) developed a non-targeted delivery platform using CdSe/ZnS quantum dot (QD) peptide bioconjugates for investigating neuronal distribution in the intact developing avian brain. The QDs (~9.5 nm) were functionalized with zwitterionic ligands (CL4) or PEG and conjugated to the cell-penetrating peptide JB571, enabling cellular uptake and endosomal escape. In *in ovo* chick embryo models, QD-peptide conjugates demonstrated widespread, non-specific distribution across neural progenitors and differentiating neurons, without perturbing key developmental markers (SOX2, TUBB3, glial markers), indicating low acute neurotoxicity. The QDs persisted transiently during early development, followed by partial clearance via the choroid plexus, illustrating natural elimination pathways. Mechanistically, the platform relies on size and peptide-mediated cell penetration rather than receptor-mediated targeting, making it suitable primarily as a research tool for tracking cellular migration and delivering biomolecules in the developing brain. Limitations include a lack of long-term toxicity assessment, limited relevance to mammalian systems, and limited direct applicability of microinjection delivery, highlighting that, while effective for developmental studies, translation to therapeutic contexts would require significant optimization (64).

Targeted delivery approaches exploit receptor-mediated transcytosis, exemplified by QDs functionalized with asparagine-glycine-arginine (NGR) peptides, which selectively bind CD13 receptors overexpressed on glioma cells, facilitating blood–brain barrier (BBB) penetration and localized accumulation (59, 68). In their study, Wang *et al.* reported CdSe/CdS/ZnS core/interlayer/shell QDs with band-gap engineering designed to enhance three-photon luminescence for deep brain imaging. The introduction of a CdS interlayer transformed the structure from type-I to quasi-type-II, enabling enhanced three-photon absorption through intrinsic piezoelectric polarization, while the ZnS outer shell passivated surface defects to maintain a high quantum yield. These QDs were PEGylated to improve biocompatibility and administered *in vivo* in mice for three-photon fluorescence microscopy (3PFM), achieving imaging of cerebral microvasculature up to 1550 μm depth

in open-skull models and 850 μm in intact-skull models. The QDs were non-targeted, relying on passive distribution and tissue penetration, with sizes controlled at the nanometer scale via the core/interlayer/shell design. Although the study demonstrated remarkable imaging depth and resolution (capillaries ~0.8 μm), limitations include potential cadmium toxicity, incomplete long-term biodistribution data, and untested applicability in larger animals or humans. Overall, this work highlights the potential of engineered QDs for non-targeted, high-resolution deep brain imaging through precise structural control and optical optimization (67). Besides, Connor *et al.* highlight the potential of non-specified QDs as a non-targeted nanoplatform for early detection of general brain changes associated with neurodegeneration. These QDs exhibit high photostability, tunable emission, and efficient tissue penetration, enabling structural and functional imaging of subcortical regions without molecular or cellular specificity. The study by Jackson *et al.* investigated the feasibility of using QDs for macrophage-mediated targeting and imaging of brain tumors, particularly gliomas. The QDs used were CdSe/ZnS core–shell QDs (~15–20 nm hydrodynamic size) labeled with PEG and surface carboxyl groups to enhance stability and biocompatibility. These QDs were efficiently phagocytosed by macrophages and subsequently trafficked to experimental intracranial gliomas in rodent models, demonstrating a "Trojan-horse" targeting strategy using immune cells rather than receptor-mediated targeting (65). *In vivo* imaging revealed the clear accumulation and co-localization of QD-labeled macrophages within glioma tissue, as confirmed by fluorescence microscopy and histological staining. This indicated that innate immune cell homing toward tumor microenvironments could be exploited for nanocarrier delivery in brain tumors. The application was diagnostic, enabling tumor visualization and delineation rather than therapeutic benefit (65).

However, limitations include the use of cadmium-based QDs, which are highly cytotoxic; the lack of long-term biodistribution data; and the absence of BBB penetration without cellular assistance. No therapeutic function or drug delivery was assessed. The study is significant historically, demonstrating one of the earliest applications of cell-mediated QD targeting in neuro-oncology. By crossing the BBB non-specifically, QDs enable high-resolution visualization of neuronal networks, hemodynamic responses, and early neurodegenerative alterations. While this approach is highly promising for diagnostic imaging, its lack of targeting limits therapeutic intervention, and concerns regarding long-term biocompatibility, biodistribution, and clearance remain. Overall, this study positions non-targeted, general QDs as a powerful tool for minimally invasive early detection and functional monitoring in neurodegenerative disease research (68). Wen *et al.* developed theranostic liposomes loaded with CdSe/ZnS QDs (QDs) and apomorphine to achieve efficient brain targeting and simultaneous bioimaging. The liposomes, with an average size of ~140 nm, encapsulated QDs in the lipid bilayer and apomorphine in the aqueous core. Cellular uptake studies demonstrated that liposomes entered brain endothelial cells via energy-dependent endocytosis, primarily through clathrin- and caveolae-mediated pathways. *In vivo* imaging in nude mice showed enhanced accumulation in the brain compared with free QDs, prolonged fluorescence retention, and reduced systemic distribution in the liver and heart. This nanoplatform enabled improved delivery of apomorphine to the brain, highlighting its potential for neurodegenerative disorders, particularly PD. Despite promising outcomes, long-term toxicity, controlled drug release profiles, and scalability for clinical translation remain limitations. Overall, this study demonstrates the feasibility of liposome-QD theranostic systems for targeted brain delivery, combining precise size control, mechanistic uptake, and imaging functionality (66). Beyond healthy models, QDs exhibit translational value in disease contexts: NIR-II QDs improve contrast in traumatic brain injury (TBI), integrin-targeted or peptide-conjugated QDs selectively accumulate in gliomas for image-guided surgery, and GQDs reduce neuroinflammation and enhance dendritic spine density in AD mouse models (69-72). Collectively, these studies demonstrate that QDs overcome key limitations of conventional probes while offering targeted, multiplexed imaging and therapeutic functionality (66, 67, 69-84). Also, in one of the comprehensive reviews, Chakraborty *et al.* highlighted the transformative potential of QDs as nanotheranostic platforms for neuro disorders, particularly glioblastoma multiforme (GBM). The authors emphasized that surface-engineered QDs, including PEGylated, antibody-functionalized, peptide-modified (e.g., RGD, transferrin), and aptamer-conjugated QDs, enable selective targeting of glioma cells via receptor-mediated mechanisms involving EGFR, integrin αvβ3, CD133, and transferrin receptors, which are overexpressed in brain tumors. Their intrinsic fluorescence properties facilitate high-resolution tumor imaging, surgical navigation, and real-time biodistribution tracking. At the same time, their functionalized surfaces enable co-delivery of chemotherapeutics (e.g., temozolomide, doxorubicin), siRNA, or photosensitizers for synergistic therapy (85). The review further discusses the role of QDs in photodynamic therapy (PDT), where near-infrared (NIR)-activated QDs induce ROS generation, leading to targeted tumor apoptosis with minimal systemic toxicity. The study reaffirms that QDs represent a highly versatile theranostic platform, uniquely capable of integrating simultaneous imaging, targeted delivery, and tumor ablation, making them strong candidates for precision medicine in neuro disorders. However, to advance toward clinical application, future research must prioritize biocompatible QD alternatives (carbon, graphene, and ZnO-based QDs), scalable synthesis, and comprehensive biosafety evaluation (85). While non-targeted carbon-, graphene-, and ZnO-based QDs have demonstrated intrinsic therapeutic benefits through spontaneous interactions with pathogenic proteins, ROS scavenging, and neuroprotective effects, their clinical translation remains constrained by limited specificity and suboptimal biodistribution. These platforms primarily rely on physicochemical surface interactions rather than biological targeting, making them effective for early-stage molecular modulation but insufficient for precise delivery, *in vivo* tracing, or controlled release. Consequently, research is progressively shifting toward functionalized and biologically targeted theranostic QDs, engineered with ligands, peptides, antibodies, or membrane-mimetic coatings, to enhance BBB penetration, receptor-specific targeting, and real-time imaging capabilities. These next-generation nanoplatforms bridge diagnosis and therapy in a

single construct, enabling molecular imaging, drug delivery, and aggregation inhibition with superior precision and reduced systemic toxicity. Thus, non-targeted QDs serve as fundamental precursors, paving the way for advanced, multifunctional theranostic systems capable of personalized and disease-modifying interventions across AD, PD, and MS (8, 9, 28, 60).

Interaction mechanisms and binding evaluation of quantum dot-based nanostructures

The interaction between carbon- and graphene-based QDs and engineered nanoceramic QDs, such as ZnO, is not governed by classical covalent binding but rather by a dynamic network of non-covalent and environment-dependent interactions. These include electrostatic interactions, hydrogen bonding, π–π stacking (particularly in graphene and carbon-based QDs), hydrophobic interactions, and coordination bonding involving surface Zn^{2+} ions in ZnO QDs. In biological environments, these interactions are further modulated by pH, ionic strength, and protein corona formation, which significantly influence the apparent affinity and stability of nanostructure assemblies.

Experimental determination of interaction strength in QD-based systems is typically indirect and relies on biophysical and spectroscopic techniques. Common approaches include fluorescence quenching assays, isothermal titration calorimetry (ITC), surface plasmon resonance (SPR), zeta potential analysis, and molecular dynamics (MD) simulations. These methods allow estimation of binding affinity and thermodynamic behavior under physiological-like conditions (86).

Although direct binding constants between carbon/graphene QDs and ZnO QDs are not systematically reported in the literature, studies of QD–biomolecule interactions report dissociation constants (Kd) of approximately 10^{-9} to 10^{-6} M, depending on surface functionalization, ligand density, and target specificity. These values indicate relatively weak, reversible interactions, consistent with adsorption-driven rather than covalent binding mechanisms.

Overall, interactions among different classes of QDs are best described as physicochemical associations governed by surface chemistry rather than fixed stoichiometric binding, highlighting the importance of surface engineering in controlling their stability, functionality, and biological performance (87, 88).

The rationale for using QDs and future perspectives

QDs are nanoscale semiconductor materials whose unique physicochemical and optical characteristics make them exceptionally promising for advanced biomedical applications, particularly in the diagnosis and therapy of neurodegenerative disorders. Importantly, their nanoscale size enables QDs to traverse the BBB, a major obstacle for conventional therapeutics, by leveraging intrinsic transport mechanisms of brain capillary endothelial cells (BCECs), thus allowing precise and targeted delivery of therapeutic and diagnostic agents into the central nervous system (CNS) (5, 89). The large and tunable surface area of QDs supports conjugation with a wide range of ligands, antibodies, peptides, or drugs, broadening their theranostic potential (6). Such functionalization enhances biostability, targeting specificity, and immune evasion, while biodegradable carbon-based QDs (CQDs) further reduce inflammation and preserve BBB integrity, improving safety profiles for *in vivo* applications (5).

QDs exhibit strong light absorption, size-tunable emission, long fluorescence lifetimes, and remarkable resistance to photobleaching, outperforming conventional organic fluorophores for real-time *in vivo* imaging and long-term cellular tracking (7, 90). Their broad excitation and narrow emission spectra enable multiplexed imaging, and fluorescence can be modulated by specific biomolecular interactions, providing high-sensitivity biosensing capabilities. For example, CQDs responsive to β-amyloid can detect early pathological changes in AD before clinical symptoms appear (8). Surface modifications, such as nitrogen doping, increase functional group density (-NH_2, -OH), thereby enhancing molecular recognition and adsorption efficiency (9). QDs also offer therapeutic advantages by modulating amyloid synthesis, inhibiting aggregation, and enabling targeted drug delivery, potentially overcoming limitations of conventional therapies (28). Multifunctional QD platforms integrating bioactive molecules exemplify this approach. For instance, fucoidan-conjugated QDs combine neuroprotective effects with targeted delivery, improving therapeutic outcomes (23). Beyond AD, QDs are being investigated for other neurodegenerative conditions: ZnO QDs deliver gene-silencing constructs targeting SNCA in PD through lysosomal escape mechanisms (91), while verapamil-loaded CQDs enhance BBB permeability, reduce oxidative stress, and attenuate neuroinflammation compared with free drugs (34), while verapamil-loaded CQDs enhance BBB permeability, reduce oxidative stress, and attenuate neuroinflammation compared with free drugs (60).

Despite these promising developments, critical challenges remain for clinical translation. Toxicity, particularly of heavy-metal-based QDs, remains a concern due to potential oxidative stress, neuronal injury, and behavioral impairments (7, 10). Toxic effects are influenced by size, composition, surface chemistry, dosage, and exposure duration. Additionally, high surface reactivity may promote aggregation, compromising stability and biodistribution. These limitations can be mitigated by surface passivation, PEGylation, and core–shell engineering (11). Successful translation also requires comprehensive safety assessment, including acute and chronic toxicity studies, pharmacokinetics, and pharmacodynamics (PK/PD) profiling to elucidate ADME characteristics, and confirmation of photostability and chemical robustness under physiological conditions (28). Improving targeting specificity through ligand conjugation (e.g., transferrin or folic acid), alongside extensive BBB permeability studies under human-relevant conditions, will accelerate clinical application. Finally, scalable and GMP-compliant synthesis is essential to bridge the gap from laboratory research to clinical use (9).

Future directions

With their ability to integrate diagnostic precision, targeted delivery, therapeutic modulation, and real-time monitoring into a single platform, QDs represent a transformative frontier in the management of neurodegenerative diseases. Their multifunctional capabilities promise earlier diagnosis, more effective interventions, and the development of

personalized, multimodal therapeutic strategies. Future research should focus on refining surface engineering, optimizing biocompatibility, and standardizing clinical evaluation protocols to translate QD-based technologies from experimental systems into safe, effective, and scalable clinical solutions. As these challenges are progressively addressed, QDs are poised to redefine the landscape of neurotherapeutics, offering new hope for conditions such as AD, PD, and beyond.

Conclusion

QDs, particularly carbon dots (CDs), offer a versatile platform for the diagnosis, imaging, and treatment of neurodegenerative diseases such as AD. Preclinical studies demonstrate their potential to inhibit protein aggregation, modulate neuroinflammation, and serve as nanosensors for early biomarker detection. However, most findings remain limited to *in vitro* or preliminary *in vivo* models, and the clinical translation of CD-based therapeutics is constrained by challenges such as BBB penetration, physicochemical optimization, biodistribution monitoring, and long-term safety assessment.

Despite these limitations, QDs offer unique advantages over conventional therapies, including targeted delivery, multifunctional theranostic capabilities, and tunable optical properties, which could enable early intervention and precise monitoring of disease progression. Future research should focus on systematic *in vivo* evaluation, optimization of non-invasive administration routes, and integration with gene or peptide-based therapies to enhance efficacy while ensuring biocompatibility. Overall, QDs constitute a promising next-generation nanoplatform, and continued interdisciplinary studies are essential to realize their full potential in the clinical management of neurodegenerative disorders.

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Authors' Contributions

K J Conceptualization, Software, Data curation, Validation, Formal analysis, Investigation, Resources, Project administration, Writing–review and editing, Data curation, Writing–original draft. L E Conceptualization, Supervision, Project administration, Writing–review and editing, Investigation. S M Conceptualization, Supervision, Project administration, Writing–review and editing, Investigation, Validation, Formal analysis. M H Conceptualization, Methodology/ Study design, Validation, Formal analysis, Investigation, Resources, Supervision, Project administration, Writing–review and editing, Data curation, Funding acquisition. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Declaration

We acknowledge the use of AI Grammarly to control structures.

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