

Carbon nanomaterials for tau targeting in Alzheimer's disease: Theranostic strategies and clinical prospects

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Abstract

Tauopathies, including Alzheimer's disease (AD), are characterized by the pathological aggregation of tau proteins, culminating in progressive neurodegeneration and cognitive decline. Conventional therapeutic strategies remain limited by inadequate blood-brain barrier (BBB) penetration, insufficient specificity for tau pathology, and lack of real-time disease monitoring. While carbon-based nanomaterials have been extensively investigated for amyloid- β related applications, their potential for tau-directed theranostics remains at an early yet rapidly advancing state. Carbon-based nanomaterials—including carbon dots, fullerenes, graphene derivatives, and carbon nanotubes—exhibit exceptional physicochemical versatility, demonstrating potential to inhibit tau aggregation, scavenge reactive oxygen species (ROS), enable precision drug delivery, and facilitate ultrasensitive detection of tau biomarkers. Their inherent capacity for BBB penetration and dual diagnostic-therapeutic functionality positions them as transformative candidates for next-generation management of tauopathies. Despite this promise, most evidence remains preclinical, and major translational challenges persist. These include long-term biocompatibility and toxicological uncertainties, lack of standardized synthesis and functionalization protocols, production scalability, and the molecular heterogeneity of tau pathology across distinct tauopathies. This review provides a comprehensive assessment of carbon nanomaterials to date in the context of tau pathology, critically examining their theranostic potential and the barriers impeding clinical translation. By delineating current limitations and strategic priorities for future research, it underscores the urgent need for coordinated interdisciplinary efforts to convert these versatile nanoplatforms from conceptual promise to clinically actionable technologies for precision tau-targeted therapy.

Keywords

Alzheimer's disease, blood-brain barrier, carbon dots, carbon nanomaterials, carbon nanotubes, fullerenes, graphene, tauopathy

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Introduction

Despite decades of research focused on amyloid- β (A β) plaques and multiple high-profile clinical trial failures, tau pathology has emerged as a more promising therapeutic target in Alzheimer's disease (AD). AD is a progressive neurodegenerative disorder and the leading cause of dementia worldwide, imposing an immense burden on patients, caregivers, and healthcare systems.¹ While traditionally linked to A β plaque deposition, increasing evidence implicates tau pathology, characterized by the abnormal aggregation and propagation of the microtubule-associated protein tau, as a central driver of neurodegeneration and cognitive decline. Intracellular neurofibrillary tangles (NFTs), composed of aggregated tau, correlate more closely with disease severity than A β plaques.^{2–4} As of 2024, no tau-targeted therapies have received regulatory approval,

though Tauvid™—a diagnostic PET imaging agent for tau pathology—has been FDA-approved.^{5,6} Multiple therapeutic approaches, including monoclonal antibodies and antisense oligonucleotides (ASOs) like BIIB080, have shown promise in early-stage trials but have not demonstrated sufficient efficacy in Phase III studies.^{2,7,8} Despite setbacks, ongoing research continues to explore novel

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strategies targeting tau phosphorylation, aggregation, and clearance mechanisms.

In this context, nanotechnology has emerged as a promising frontier in neurotheranostics, offering integrated tools for targeted drug delivery, real-time molecular diagnostics, and modulation of pathological protein aggregation.^{9–11} Among various nanomaterials, carbon-based nanostructures have garnered particular interest owing to their distinctive electrochemical and optical characteristics, exceptional sensitivity and selectivity, high surface-to-volume ratio, and controllable nanoscale dimensions, alongside versatile functionalization potential.^{12–14} These materials exhibit multifaceted potential in addressing tau pathology by inhibiting tau aggregation, promoting clearance, enhancing targeted delivery of therapeutic agents, and enabling sensitive biomarker detection. Notably, their dual roles in both therapeutic modulation and diagnostic imaging position them as promising theranostic platforms for AD and related tauopathies such as progressive supranuclear palsy (PSP) or corticobasal degeneration.

As the molecular understanding of tau biology expands—particularly its isoform diversity, post-translational modifications, and prion like propagation—the integration of nanotechnological approaches holds promise for advancing tau-directed interventions. While several reviews^{13–18} have examined carbon nanomaterials in AD, they have largely focused on A β aggregation, biosensing applications, or general neuroprotective effects, with limited attention to tau-specific mechanisms and theranostic applications. Consequently, focused evaluations of carbon nanomaterials for tau pathology remain scarce.

This review addresses this gap by critically assessing recent advances in carbon nanomaterials for modulating tau pathology. The discussion focuses on a range of materials, including carbon nanotubes (CNTs), graphene derivatives, fullerenes, carbon dots (CDs), with particular emphasis on their theranostic potential in AD. We highlight their mechanisms of action in regulating tau aggregation, delivering neuroprotective agents, and enabling ultrasensitive biomarker detection, while also discussing translational challenges such as biocompatibility, blood-brain barrier (BBB) permeability, and isoform-selective targeting. Finally, we outline strategic directions for engineering multifunctional, scalable, and clinically viable carbon nanomaterial platforms for integrated management of tauopathies.

Molecular basis of tau dysfunction and its implications in AD

Abnormal protein aggregation is a defining hallmark of numerous neurodegenerative disorders, including AD.^{19,20} In AD, this pathological process involves a complex interplay of molecular mechanisms, such as A β accumulation, neuroinflammation, oxidative stress, synaptic dysfunction, and most notably, tau pathology.^{21–23} While the extracellular buildup of A β plaques has historically received substantial

attention, increasing evidence highlights the critical role of tau pathology in driving neuronal degeneration and disease progression. Tauopathies, the broader class of neurodegenerative diseases marked by pathological tau accumulation, can be broadly classified into two categories: primary tauopathies, such as Pick's disease, PSP, and corticobasal degeneration (CBD), in which tau dysfunction is the primary driver of disease; and secondary tauopathies, including AD, where tau abnormalities arise as a downstream consequence of other initiating events—most notably, A β accumulation.²⁴ Although A β may initiate early pathophysiological changes in AD, it is tau pathology that shows a stronger correlation with the extent of neurodegeneration and clinical severity, particularly cognitive decline, highlighting its central role in disease progression.^{25,26}

Tau, a microtubule-associated protein, undergoes a series of pathological modifications that transform it from a stabilizing cytoskeletal component into a neurotoxic species.²⁷ Tau is encoded by the *MAPT* gene located on chromosome 17. Through alternative splicing, *MAPT* gives rise to six major isoforms in the adult human brain.^{28,29} Under normal physiological conditions, tau is primarily localized in axons, where it stabilizes microtubules, maintains neuronal polarity, facilitates axonal transport, and supports synaptic plasticity.³⁰ These functions are critical for sustaining the structural and functional integrity of neurons. In AD and related tauopathies, tau undergoes extensive post-translational modifications, particularly hyperphosphorylation, which reduces its affinity for microtubules. This leads to cytoskeletal destabilization and accumulation of mislocalized tau in the somatodendritic compartment. The dislodged, misfolded tau proteins become prone to aggregation into paired helical filaments (PHFs), which subsequently form intracellular NFTs—a pathological hallmark of AD. The formation of tau aggregates results in both loss-of-function, due to the compromised ability to stabilize microtubules, and gain-of-function toxicity, as aggregates interfere with intracellular signaling, impair synaptic function, and contribute to neuronal death.^{31,32} These pathological changes are visually summarized in Figure 1, which illustrates the progression from normal tau function to the multifaceted tau-driven neuronal damage characteristic of AD.

One of the most striking features of tau pathology is its ability to propagate in a prion-like manner.^{33,34} Misfolded tau can act as a seed, inducing the misfolding and aggregation of native tau in neighboring cells. This intercellular transmission may occur via multiple mechanisms, including extracellular vesicles (e.g., exosomes), direct synaptic connections, and tunneling nanotubes (TNTs)—actin based cytoplasmic bridges that enable the transfer of pathological tau aggregates between cells and facilitate the prion-like spread of tau pathology.³⁵ This behavior may explain the stereotyped spatial and temporal progression of tau pathology observed in AD. Several interrelated mechanisms contribute to tau-mediated toxicity disrupting neuronal homeostasis. One key feature is the mislocalization of tau from axons to

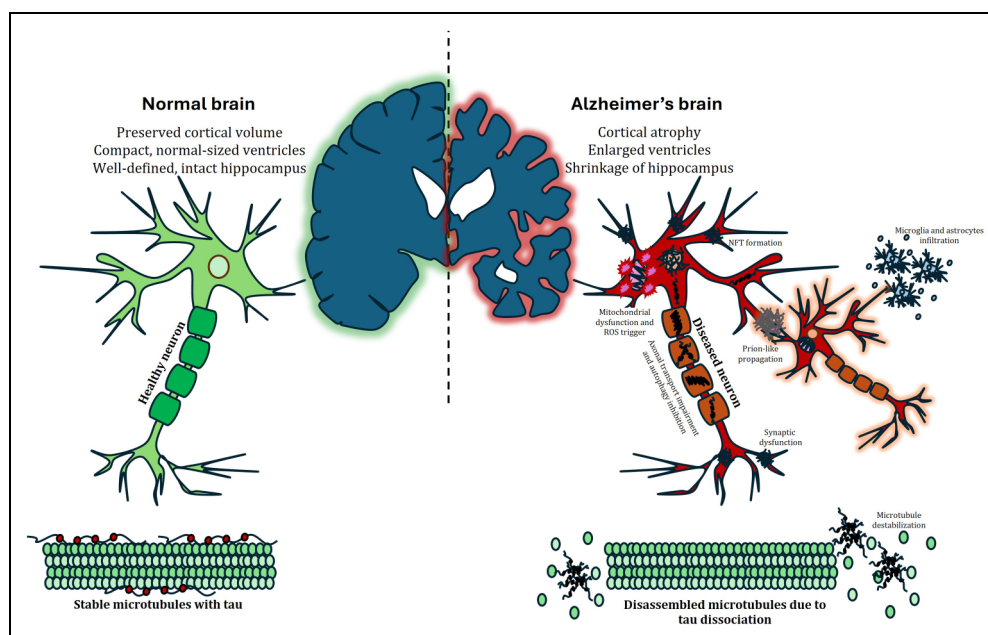


Figure 1. Pathological hallmarks and progression of tauopathies in Alzheimer's disease. The healthy brain (left) exhibits intact neurons with stable microtubules and proper tau function. As pathology progresses, tau becomes hyperphosphorylated and detaches from microtubules, resulting in microtubule destabilization, impaired axonal transport and mitochondrial dysfunction. In the diseased state (right), the brain displays cortical atrophy, and the neurons exhibit severe tau aggregation, formation of neurofibrillary tangles, synaptic loss, and neuroinflammation driven by reactive microglia. Extracellular tau release and spreading, membrane disruption, and accumulation of toxic tau species further exacerbate neuronal damage and cognitive decline. This sequence illustrates the multifactorial and progressive nature of tau pathology in Alzheimer's disease.

the somatodendritic compartment, where it interferes with postsynaptic signaling and impair synaptic plasticity.^{36,37} Additionally, isoform imbalance-caused by aberrant alternative splicing or dysregulation of the *MAPT* gene-can disrupt the normal 3R/4R tau (referring to tau protein isoforms with three or four microtubule-binding repeats, respectively) ratio, thereby promoting aggregation.³⁸ A wide array of post-translational modifications, including acetylation, truncation, ubiquitination, and glycation, further modulate tau's aggregation propensity and interactions with intracellular components.^{39,40} Compounding these effects are deficits in protein clearance and trafficking pathways, such as impaired autophagy and proteasomal degradation, which hinder the removal of pathological tau.⁴¹ Together, these interlinked mechanisms drive synaptic dysfunction, neuronal loss, and the progressive neurodegeneration characteristic of tauopathies. A deeper understanding of the molecular and cellular dynamics of tau-from its genetic origins to its pathological propagation-provides essential insights into the mechanisms underlying AD and other tauopathies, guiding the development of targeted therapeutic interventions.

The complexity of tau pathology, with its intracellular localization, diverse isoforms, multiple aggregation pathways, and prion-like spreading mechanisms, presents formidable challenges for conventional therapeutic approaches. Traditional drug delivery faces significant barriers in reaching

intracellular tau targets, while the heterogeneity of tau species across different disease stages demands multifunctional intervention strategies. These limitations underscore the need for innovative therapeutic platforms that can simultaneously address multiple aspects of tau pathology while providing enhanced delivery capabilities and real-time monitoring functions.

Molecular strategies and translational barriers in targeting tau pathology

Given its central role in AD pathology, tau has emerged as a promising therapeutic target. A wide array of strategies is currently under development, aiming to counteract tau pathology by modulating its expression levels, altering post-translational modifications, intervening aggregation dynamics, enhancing clearance mechanisms, and mitigating the downstream functional consequences of tau toxicity.^{6,42-45} Gene expression modulation approaches include the use of ASOs^{46,47} to reduce tau protein levels by targeting microtubule-associated protein tau (*MAPT*) mRNA or its upstream regulators, such as Tau-tubulin kinase 1 (TTBK1), CRISPR-CAS9-based genome editing^{48,49} to silence or modify the *MAPT* gene and alter tau's post translational modifications, and splicing modulators⁵⁰⁻⁵² to restore the physiological 3-repeat to

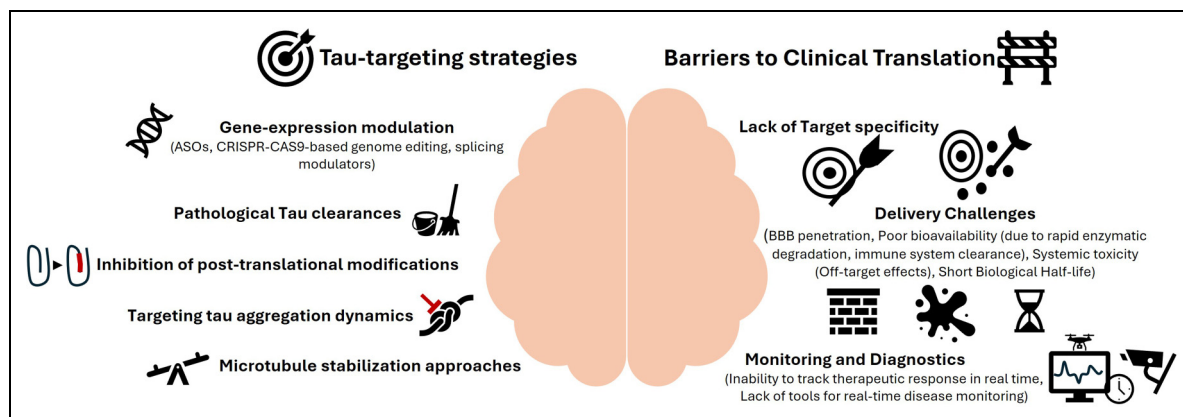


Figure 2. Schematic representation of tau-targeting therapeutic strategies and the barriers to their clinical translation.

4-repeat (3R:4R) tau isoform ratio, which is often dysregulated in tauopathies. Inhibition of post-translational modifications constitutes another mechanistic class, primarily targeting the hyperphosphorylation of tau through the inhibition of key kinases such as glycogen synthase kinase-3 β (GSK-3 β) and cyclin-dependent kinases (CDKs).^{53–56} Addressing tau aggregation dynamics involves employing small molecules to prevent or disrupt tau-tau interactions and the formation of insoluble fibrils and NFTs.^{57–59} Pathological tau clearances encompasses both immunotherapeutic approaches, which use monoclonal antibodies to neutralize extracellular tau species, and agents that enhance intracellular degradation pathways, such as autophagy or the ubiquitin-proteasome system.^{60–62} Finally, microtubule stabilization approach aims to compensate for tau's loss of function by reinforcing microtubule structure and dynamics, which are critical for neuronal integrity and transport.^{63,64} These diverse therapeutic strategies, along with the major translational barriers they face, are illustrated in Figure 2.

Despite the diversity of tau-targeting strategies, ranging from gene expression modulation and post-translational modification inhibition to immunotherapy and aggregation blockers, their clinical translation remains hampered by critical challenges, particularly in delivery and disease monitoring. A major barrier lies not in the mechanisms themselves, but in their limited ability to effectively reach and act within the brain. Many therapeutic agents, including nucleic acid-based drugs such as small interfering RNAs (siRNAs) and ASOs, face poor bioavailability due to rapid enzymatic degradation and immune clearance. Furthermore, most therapeutic molecules struggle with inadequate BBB penetration, systemic toxicity, short biological half-life, or lack of specificity to tauopathies. An additional complication lies in the inability to monitor therapeutic response and disease progression in real time, which is critical for precision medicine.

To address these issues, theranostic platforms-technologies that integrate therapeutic delivery with diagnostic imaging-have gained significant attention. Among the

promising solutions, nanotechnology, particularly carbon-based nanomaterials, has emerged as a versatile tool. These materials not only modulate disease mechanisms such as tau aggregation and oxidative stress but also enable targeted drug delivery and in situ diagnostics, offering a multifaceted approach to tau-directed therapies.

Theranostic potential of carbon nanomaterials in tauopathy management for AD

Carbon dots (CDs)

CDs are a class of zero-dimensional carbon nanomaterials typically less than 10 nm in size. They exhibit strong photoluminescence, quantum confinement effects, and excellent water dispersibility, making them valuable for biomedical imaging, drug delivery, and neurotherapeutic applications. These physicochemical characteristics have been harnessed in the synthesis of curcumin-derived carbon quantum dots (Cur-CQDs), produced via a green one-step dry heating process to retain curcumin's bioactivity while addressing its limitations in solubility and bioavailability.⁶⁵ In cellular models, Cur-CQDs-particularly Cur CQDs-210-demonstrated strong biocompatibility and significantly reduced okadaic acid-induced tau hyperphosphorylation. This inhibitory effect is thought to stem from the preserved functional groups in Cur-CQDs, which may modulate key kinases (e.g., GSK-3 β , CDK5) and phosphatases (e.g., PP2A), while also exerting antioxidant and anti-inflammatory actions. Another promising example involves carbon dots derived from Congo red (CRCDs), synthesized with citric acid, which have demonstrated dual inhibitory effects against both tau and A β aggregation.⁶⁶ Among the synthesized variants, CRCD1 showed the strongest inhibitory activity, with IC₅₀ values of 0.2 μ g/mL for tau and 2.1 μ g/mL for A β and maintained over 70% cell viability in HEK 293 cells at 100 μ g/mL, indicating acceptable biocompatibility. In contrast, CRCD3 exhibited the highest

BBB permeability, as confirmed in zebrafish model, likely due to its enhanced amphiphilicity from high citric acid content. Together, these findings position CRCDs as versatile candidates for multifunctional roles in AD therapy.

Carbon nitride dots (CNDs) have emerged as promising candidates for AD therapy due to their multifunctional properties. In one study,⁶⁷ CNDs were fractionated to investigate structure-dependent inhibition of tau aggregation. The results revealed that hydrophobic interactions play a pivotal role in their anti-tau activity, with less polar CND fractions exhibiting stronger inhibition – an effort corroborated by molecular dynamics simulations. Beyond modulating tau pathology, CNDs also demonstrated effective BBB permeability via passive diffusion and notable reactive oxygen species (ROS)-scavenging activity, highlighting their dual potential to address both protein aggregation and oxidative stress. A related study⁶⁸ explored the use of CNDs and black carbon dots (B-CDs) as nanocarriers for memantine hydrochloride (MH), an FDA-approved drug for moderate to severe AD. Both types of carbon dots were successfully conjugated with MH and evaluated for their therapeutic enhancement. While both conjugates demonstrated the ability to inhibit tau aggregation, B-CDs-MH exhibited the strongest tau aggregation inhibitory effect. Notably, CNDs-unlike B-CDs-demonstrated effective BBB permeability in zebrafish model, positioning them as more suitable carriers for brain-targeted drug delivery. Together, these studies highlight CNDs as multifunctional platforms that not only modulate pathological protein aggregation and oxidative stress but also facilitate targeted therapeutic delivery within the central nervous system.

In summary, carbon dots like Cur-CQDs, CRCDs, and CNDs represent a novel class of nanomaterials with considerable potential for therapeutic application in Alzheimer's disease. Their ability to modulate tau aggregation, provide antioxidant effects, and improve drug delivery to the brain positions them as promising candidates for AD treatment (Figure 3). Additionally, CNDs demonstrate effective BBB permeability and ROS-scavenging activity, further enhancing their therapeutic potential. However, further investigation into their pharmacokinetics, safety profiles, and long-term therapeutic outcomes is essential before they can be considered for clinical use.

Fullerenes

Fullerenes (e.g., C₆₀) are spherical carbon nanostructures composed entirely of sp²-hybridized carbon atoms. Their unique cage-like architecture allows them to act as efficient radical scavengers and potential modulators of protein aggregation relevant to neurodegenerative diseases. Although direct research on fullerenes in tauopathy is limited, several studies have explored their interaction with amyloid- β peptides, which share structural similarities with tau proteins, particularly in their β -sheet-rich aggregation pathways.^{69–71}

Fullerenes, notably C₆₀, have been shown to inhibit β -sheet formation and aggregation of A β peptides by interacting with their hydrophobic regions,⁷² suggesting potential therapeutic effects in tau-related pathologies. Given the structural and mechanistic parallels between A β and tau aggregation,⁷³ it is plausible that fullerenes could exert similar anti-aggregative effects on tau fibrillation. However, direct studies on fullerene-tau interactions are still needed to confirm this potential and guide future therapeutic exploration.

In addition to their anti-aggregative properties, fullerene-based enzyme-free sensors for acetylcholine (ACh) detection are highly relevant to tauopathies, particularly AD, where cholinergic dysfunction is key pathological feature. A fullerene-histidine-serine-nickel (F-HS-Ni) catalyst has demonstrated effective electrocatalytic oxidation of ACh, enabling sensitive detection in serum samples.⁷⁴ Since ACh levels are closely linked to cognitive decline and tau pathology progression,^{75,76} such detection platforms may serve as valuable tools for monitoring disease stages and therapeutic efficacy in tauopathies. Acetylcholinesterase (AChE), an esterase responsible for hydrolyzing ACh, represents a key therapeutic target in AD due to its central role in regulating cholinergic transmission.⁷⁷ Multiadduct derivatives of C₆₀ fullerenes have been reported in a recent study⁷¹ to act as potential AChE inhibitors, exhibiting concentration-dependent inhibition with notable effects between 8 and 25 μ M. By attenuating AChE activity, these fullerene derivatives may help preserve cholinergic balance and, in turn, exert indirect effects on tau pathology, providing an additional avenue for therapeutic intervention in AD (Figure 4).

Fullerene C₆₀ has also shown promise in improving memory impairment in AD rat models,⁷⁸ suggesting potential neuroprotective effects through its antioxidant properties. The structure of C₆₀, rich in double bonds, makes it an efficient radical scavenger, potentially mitigating oxidative stress that contributes to tau protein hyperphosphorylation and aggregation. This highlights fullerene's therapeutic potential in reducing tau-related neurodegeneration by counteracting oxidative damage.

One significant advancement in the biomedical application of fullerenes is the development of water-soluble fullerene derivatives, such as the harmonized-hydroxylated fullerene-water complex (3HFWC).⁷⁹ Functionalized with hydroxyl groups (C₆₀(OH)_x) and encapsulated in protective water layers (C₆₀(OH)_{36 $\pm$ 12}@(H₂O)_{144–2528}), 3HFWC overcomes issues related to solubility and aggregation, improving fullerene's biocompatibility and reducing its potential toxicity. This makes 3HFWC a promising candidate for therapeutic applications in tauopathies and other neurodegenerative diseases.

Studies on fullerene-based compounds in tauopathies remain limited. Existing work demonstrates that fullerenes possess antioxidant properties, inhibit A β aggregation *in vivo*, and can inhibit AChE and detect ACh levels in

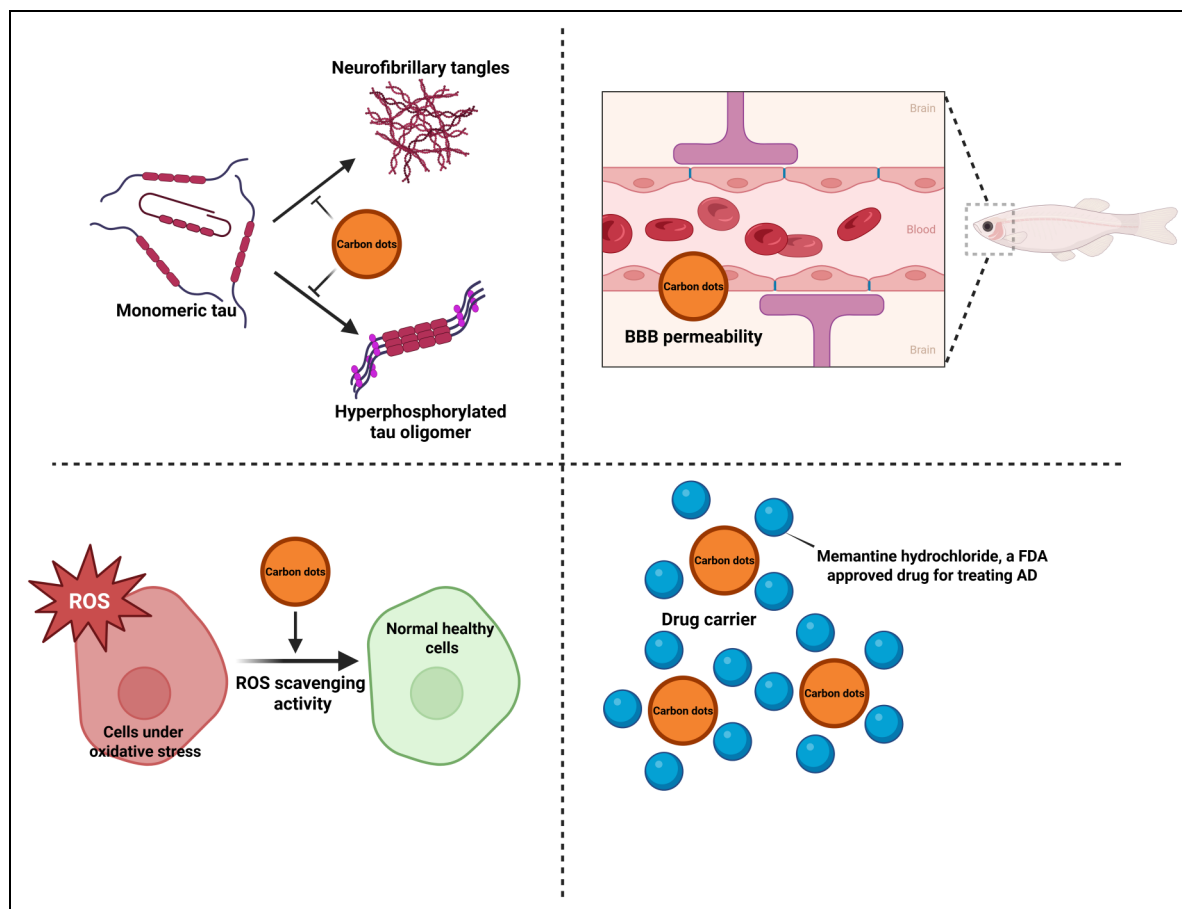


Figure 3. Therapeutic potential of carbon dots (CDs) in tauopathy. CDs inhibit tau aggregation and hyperphosphorylation, reduce oxidative stress, and protect neuronal cells from degeneration. Their high biocompatibility, antioxidant capacity, and blood-brain barrier permeability make them effective nanoplatforms for targeted modulation of tau pathology in Alzheimer's disease. Created in BioRender. Lee H (2025) <https://BioRender.com/v6ativa>.

vitro. While these largely preclinical findings suggest possible relevance to tau pathology, direct evidence for fullerene–tau interactions and cholinergic pathway modulation is still lacking, warranting targeted investigations to clarify their therapeutic potential in tauopathies. Conceptually, fullerene systems capable of ACh detection and AChE inhibition could be engineered as real-time modulators of cholinergic function, offering a novel strategy to restore ACh balance and mitigate tau-related deficits in AD.

Graphene and derivatives (graphene oxide (GO), reduced graphene oxides (rGO), and graphene quantum dots (GQDs))

Graphene and its derivatives, such as graphene oxide (GO), reduced graphene oxide (rGO), and graphene quantum dots (GQDs), are two- and zero- dimensional carbon-based nanomaterials known for their exceptional electrical conductivity, surface area, and biocompatibility. These properties enable their use in biosensing platforms and as

modulators of protein aggregation pathways. Graphene oxide (GO) and rGO-based electrochemical biosensors have shown great promise for the sensitive detection of tau biomarkers such as Tau-441 in AD. These sensors utilize graphene's high surface area, conductivity, and biocompatibility to immobilize tau-specific antibodies, enabling precise tau detection in human serum and cerebrospinal fluid. For instance, an rGO-AuNPs nanocomposite-based biosensor functionalized with 11-mercaptopundecanoic acid (11-MUA) achieved a detection limit of 0.091 pg/mL for Tau-441, demonstrating excellent reproducibility and selectivity in clinical samples.⁸⁰ Fluorescence-based immunosensors utilizing GO conjugated with anti-tau antibodies have demonstrated significant potential in detecting tau-441 protein.⁸¹ By leveraging π - π stacking and hydrophobic interactions between GO and FITC-labelled tau, these sensors offer a wash-free, linker-free approach with a limit of detection of 0.14 pmol/mL (~6.4 ng/mL). This method provides a specific, cost-effective, and clinically viable diagnostic tool for early tauopathy detection.

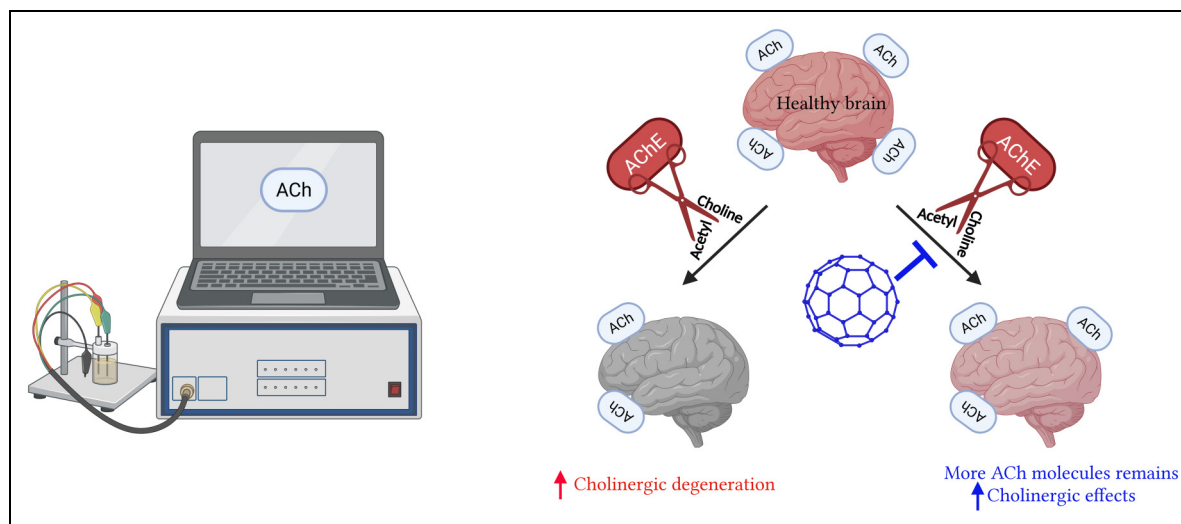


Figure 4. Theranostic relevance of fullerene in tauopathy. Fullerene derivatives facilitate ACh sensing and inhibit AChE activity, enabling assessment of cholinergic dysfunction linked to tau pathology. Created in BioRender. Lee H (2025) <https://BioRender.com/bf572kd>.

Graphene-based field-effect transistor (GFET) biosensors have become an essential tool for detecting tau proteins at extremely low concentrations. These sensors exploit graphene's unique electrical properties, enabling ultra-sensitive, single-molecule detection of tau, A β and α -synuclein. With detection limits as low as 1–10 pM, GFET biosensors can differentiate diseased from healthy brain tissues, making them ideal for point-of-care diagnostics in tauopathies and related neurodegenerative disorders.⁸² A linker-free, patterned graphene field-effect transistor (FET) sensor that utilized edge defects for direct antibody immobilization has shown a detection limit as low as 10 fg/mL for tau proteins.⁸³ The elimination of traditional linkers, along with improved charge transfer at defect sites, enhances sensor performance and reliability, even in high-ionic strength environments. This approach represents a promising strategy for ultra-sensitive and reliable tau detection.

A nanoimmunosensor utilizing GO and amine-functionalized dendrimers has been developed for the simultaneous detection of Tau proteins and Myelin Basic Protein (MBP) in cerebrospinal fluid (CSF) and serum from multiple sclerosis (MS) patients.⁸⁴ The GO/pPG/anti-MBP/anti-Tau nanoimmunosensor demonstrated detection limits of 0.30 nM for MBP and 0.15 nM for Tau proteins, making it highly suitable for clinical neurodiagnostic use. Complementing this, a GO-based surface-enhanced Raman scattering (SERS) platform functionalized with anti-tau and anti- β amyloid antibodies enables the simultaneous capture and ultrasensitive detection of multiple AD biomarkers directly from whole blood, achieving over 98% capture efficiency and a detection limit of 0.15 ng/mL for tau protein.⁸⁵ Together, these platforms underscore the versatility of GO in multi-biomarker detection, potentially aiding in the diagnosis

and monitoring of both tauopathies and other neurodegenerative disorders. The exfoliation of GO into single layers significantly improves its dispersion, surface area, and interaction with biological molecules, such as tau-specific antibodies.⁸⁶ This is commonly achieved using 1,3,6,8, pyrenetetrakisulfonic acid, which helps in separating the GO layers while introducing functional groups that enhance interactions with biomolecules. The addition of Cu²⁺ ions further stabilizes the reducing GO structure, improving its conductivity and electrochemical performance. These enhancements make GO a highly effective platform for biosensors, enabling highly sensitive tau detection in diagnostic applications such as blood or cerebrospinal fluid analysis for tauopathies.

In addition to graphene-based platforms, new developments in electrochemiluminescence (ECL) technology offer another promising approach for early AD detection. A study presents an ECL immunosensor for the detection of Tau protein in serum, utilizing gold nanostars decorated on graphite like carbon nitride nanosheets (AUNS@g-CN) to enhance ECL activity through electrocatalytic and surface plasmon effects.⁸⁷ This immunosensor demonstrates high sensitivity, with a detection range from 0.1 to 100 ng/mL and a low limit of detection of 0.034 ng/mL. Such attributes position this system as a promising tool for early AD diagnosis, specifically in detecting Tau levels in human serum.

Beyond their diagnostic applications, graphene-based materials-including GO, and GQDs-have also demonstrated therapeutic potential. Notably, GQDs have been shown to inhibit tau fibrillization and disassemble performed tau filaments, in vitro, owing to their unique ability to engage in both electrostatic interactions and π - π stacking with tau proteins⁸⁸ (Figure 5). GQDs with different surface charges, such as negatively charged Cys-GQDs, exhibit enhanced

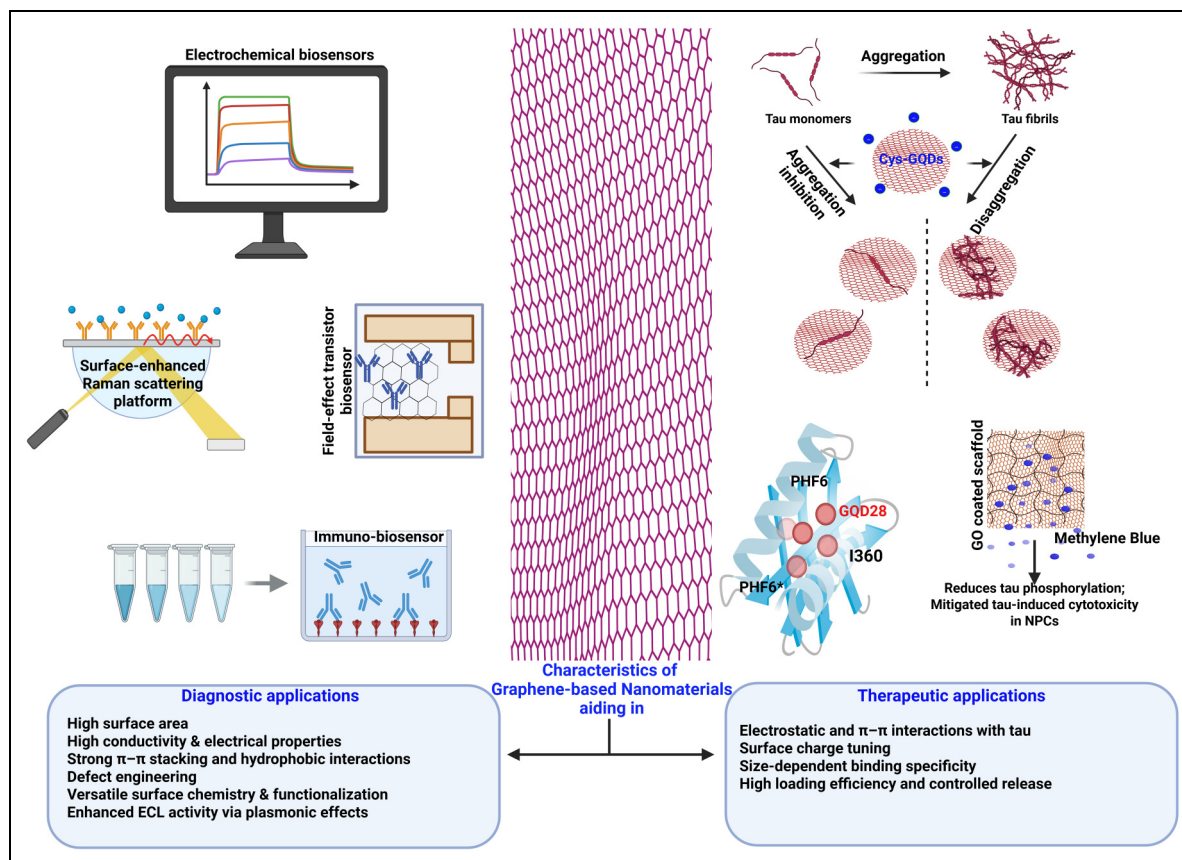


Figure 5. Graphene-based nanomaterials for tau detection and modulation. Graphene and its derivatives, including graphene oxide and graphene quantum dots, enable ultrasensitive detection of tau aggregates through electrochemical and spectroscopic biosensing platforms. Additionally, graphene quantum dots disrupt tau fibrillization and promote disaggregation, highlighting their combined diagnostic and therapeutic utility. Created in BioRender. Lee H (2025) <https://BioRender.com/7e0oc45>.

inhibitory effects by interacting with the positively charged repeat domains of tau fibrils, which is key in modulating tau aggregation and toxicity. In contrast, positively charged GQDs like EDA-GQDs exhibit reduced inhibitory efficiency due to charge repulsion and pose higher cytotoxic risks, limiting their therapeutic potential compared to the safer Cys-GQDs. Further research has expanded the potential of GQDs in targeting tau aggregates, where they have shown promising results in computational docking studies.⁸⁹ Two different sizes of GQDs, GQD7 and GQD28, were docked to various tau protein structures—including monomers, straight filaments, and PHFs. GQD28 exhibited strong, specific interactions with aggregation-prone motifs such as PHF6 (³⁰⁶VQIVYK³¹¹) region and the protofibril interface, critical for tau aggregation and disaggregation, including tau imaging sites like I360, while GQD7 displayed broader binding behavior by targeting both PHF6 and PHF6* (²⁷⁵VQIINK²⁸⁰) hexapeptide regions. Due to their size-dependent binding specificity, GQDs show strong potential as both therapeutic agents, by preventing or disassembling tau aggregates, and diagnostic tools, by selectively binding regions critical for tau imaging in AD.

GO has been employed to enhance the loading efficiency and release of methylene blue (MB) from PLGA nanofibrous scaffolds, overcoming the weak interaction between PLGA and MB.⁹⁰ Controlled MB release from GO-coated scaffolds effectively reduced tau phosphorylation and mitigated tau-induced cytotoxicity, thereby supporting the survival of neural progenitor cells. This approach illustrates the therapeutic promise of GO-based scaffolds for targeted delivery of neuroprotective molecules in tauopathies.

Graphene-based platforms excel in ultra-sensitive tau detection and offer emerging therapeutic value through GQDs. Size, charge, and surface chemistry critically influence both efficacy and cytotoxicity. As such, rational design and functional tuning of GQDs will be essential for achieving theranostic efficacy with minimal adverse effects, particularly in vivo.

Carbon nanotubes (CNTs)

CNTs are cylindrical, one-dimensional carbon nanostructures composed of rolled graphene sheets. Depending on their wall number (single- or multi-walled), they exhibit

tunable mechanical, electrical, and chemical properties, supporting their role as nanocarriers and biosensors in neurological applications. Single-walled carbon nanotubes (SWCNTs) have shown significant promise as drug carriers for AD due to their ability to preferentially target lysosomes, the pharmacological organelles, while minimizing mitochondrial uptake at controlled doses.⁹¹ This targeted delivery system ensures effective brain release of ACh, indirectly mitigating tau-related neurodegeneration by improving cognitive function, as free ACh cannot cross the BBB due to its strong polarity and rapid decomposition in blood.

In addition to their potential for drug delivery, CNTs possess unique physiochemical properties that allow them to interact with tau proteins in ways that can disrupt their structure, providing both opportunities and challenges in the context of neurodegenerative diseases.⁹² Specifically, SWCNTs, with their more hydrophilic surface, interact with tau proteins through hydrogen bonding, inducing more significant disruption to tau's tertiary structure compared to multi-walled carbon nanotubes (MWCNTs) (Figure 6). MWCNTs, being more hydrophobic, promote tau aggregation without significant structural changes. While both SWCNTs and MWCNTs can induce cell death, SWCNTs are more likely to trigger apoptosis, whereas MWCNTs are associated with necrosis. These distinct cytotoxic profiles suggest that CNTs can be strategically used for targeted drug delivery, but careful regulation is essential to minimize harmful effects. To optimize the safety and efficacy of CNTs in drug delivery for neurological conditions, their interactions with tau proteins and neuronal cells must be meticulously studied, ensuring that these interactions do not exacerbate or accelerate neurodegenerative processes.

Moreover, defective autophagy in AD accelerates tau accumulation, leading to neuronal damage.^{93–96} Preclinical evidence suggests that SWCNTs may help modulate autophagic activity and attenuate tau buildup. Functionalized SWCNTs were found to restore autophagy in primary glia from CRND8 mice expressing mutant human amyloid precursor protein (APP), likely via mTOR pathway modulation and improved lysosomal activity, facilitating tau aggregate clearance.⁹⁷ While these findings are promising, the evidence remains preliminary and confined to preclinical models; further investigations are required to validate the therapeutic potential of CNTs in enhancing autophagy and providing neuroprotection in tauopathies such as AD.

In addition to their therapeutic potential, CNTs, have garnered attention for enhancing tau detection in diagnostic platforms, including surface plasmon resonance (SPR), electrochemical immunosensors, aptamer-functionalized electrodes, and multiplexed SWCNT arrays, achieving ultrasensitive detection from femtomolar to picomolar levels in human plasma and serum. When conjugated

with antibodies, MWCNTs significantly enhance tau detection sensitivity in SPR-based biosensing, reaching the picomolar range, due to their large surface area and mass, which facilitate better binding and effective amplification.⁹⁸ This integration of MWCNTs into SPR platforms holds great promise for developing highly sensitive and specific diagnostic methods for tau quantification, which could transform the detection of AD biomarkers. For instance, a novel electrochemical immunosensor for detecting the phosphorylated Tau181 (p-Tau181) biomarker was developed using a carbon screen-printed electrode (C-SPE) modified with platinum nanoparticle-coated MWCNTs (MWCNTs-PAH/Pt).⁹⁹ This sensor exhibited a detection range from 8.6 to 1100 pg/mL and a detection limit of 0.24 pg/mL. An amine-functionalized aptamer on MWCNT electrode enabled sensitive tau detection with a 1 fM limit of detection across a 1 fM to 1 nM range ($R^2 = 0.9846$).¹⁰⁰ The sensor specifically detected tau in human serum, highlighting its potential for monitoring anesthesia-induced tau fluctuations and related neurodegenerative effects. A multiplexed electrical sensing platform using densely aligned SWCNT films achieved ultrasensitive detection of tau biomarkers (t-tau and p-tau181) in human plasma.¹⁰¹ The unidirectional, closely packed SWCNT arrangement minimizes tube-to-tube junctions and ensures uniform conductivity, thereby enhancing signal reliability and femtomolar-level sensitivity. By quantifying tau and composite biomarker ratios (t-tau/ $A\beta_{42}$, p-tau/ $A\beta_{42}$), the platform effectively distinguished AD patients from healthy controls, highlighting its promise for early, tau-centered AD diagnosis. Despite the promising results, challenges such as nanotube aggregation, batch-to-batch variability, and the need for improved SPR sensitivity to meet clinical requirements in the picomolar range must be addressed for optimal use in tauopathy diagnostics.

Each class of carbon-based nanomaterials exhibits distinct strengths and limitations in addressing tau-related therapeutic and diagnostic challenges. CDs and CNDs demonstrate excellent biocompatibility, antioxidant activity, and effective BBB permeability, making them promising multifunctional agents; however, their limited structural stability and rapid systemic clearance may constrain sustained therapeutic efficacy. Fullerenes possess strong radical scavenging and enzyme-inhibitory properties, yet their inherent hydrophobicity and scarce tau-specific data hinder translational potential. Graphene derivatives, particularly GQDs, exhibit potent tau disaggregation and high diagnostic sensitivity, though cytotoxicity and long-term accumulation remain concerns. GO offers exceptional surface area and conductivity advantageous for biosensing applications but requires precise surface functionalization to ensure biocompatibility and molecular selectivity. CNTs provide remarkable electrical and mechanical characteristics suitable for both biosensing and drug delivery platforms; nonetheless, their toxicity,

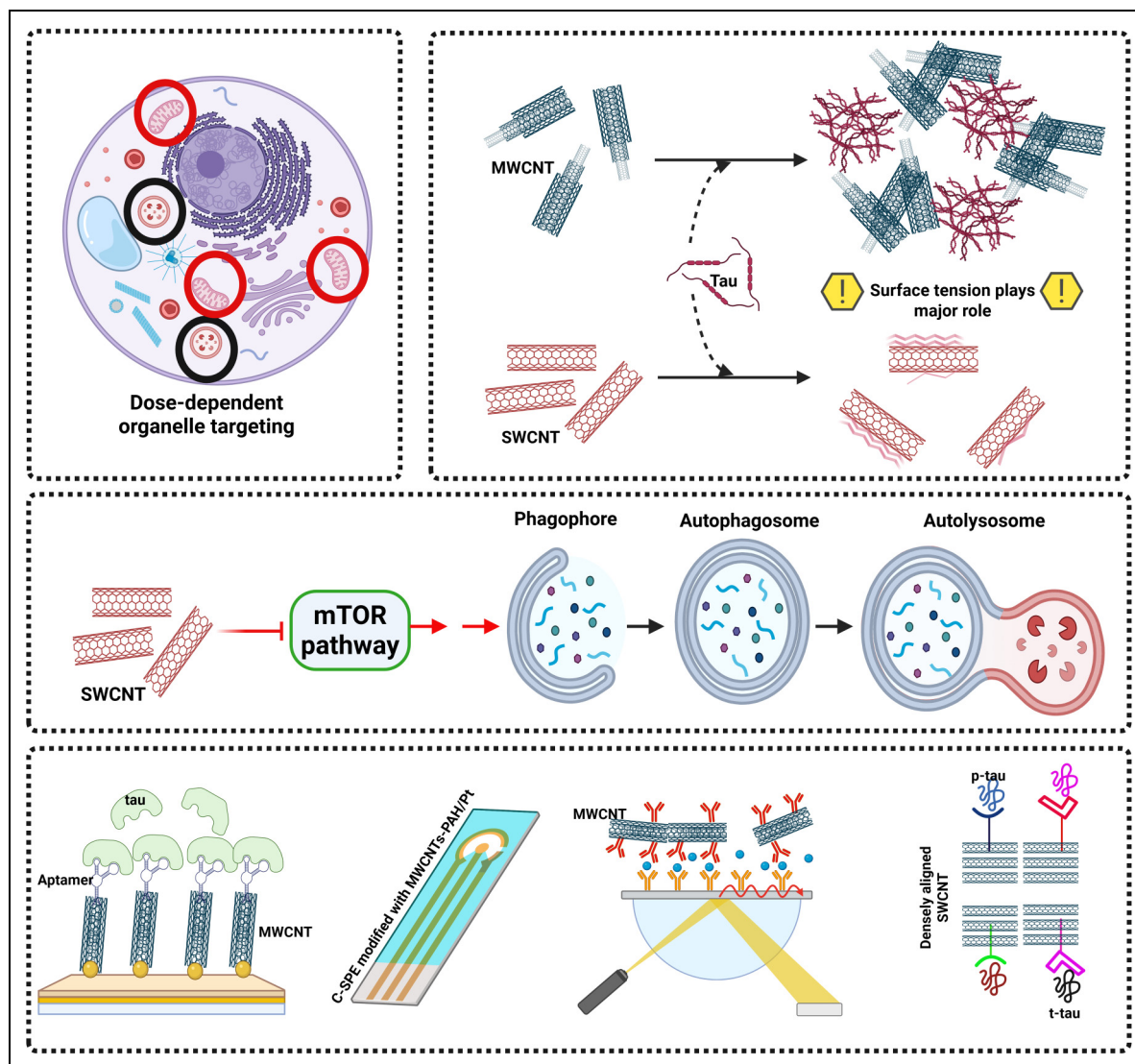


Figure 6. Theranostic applications of carbon nanotubes (CNTs) in tauopathy. CNT-based biosensors enable highly sensitive detection of tau, supporting diagnostic monitoring of disease progression. Therapeutically, CNTs promote autophagic clearance of tau and attenuate tau-induced toxicity, demonstrating dual diagnostic and therapeutic potential. Created in BioRender. Lee H (2025) <https://BioRender.com/ye8xq6j>.

aggregation tendency, and batch variability pose significant limitations. In comparison, CDs and CNDs appear most favorable for safe, multifunctional therapeutic use, whereas GQDs and CNTs excel in ultra-sensitive diagnostic applications. Fullerene and GO occupy an intermediate position, bridging therapeutic and biosensing capabilities. A summary of carbon nanomaterial-based theranostic strategies targeting tau pathology is presented in Table 1.

Challenges and future directions

As previously discussed, traditional tau-targeting approaches face persistent limitations in brain delivery, molecular

specificity, and real-time disease monitoring. Carbon-based nanomaterials hold immense promise for overcoming many of these barriers due to their unique physicochemical properties, including potential for BBB penetration, molecular recognition, and theranostic capabilities. However, their clinical translation is hindered by several key challenges that must be resolved to enable widespread adoption in therapeutic settings.

One of the foremost challenges lies in biocompatibility and long-term safety. While several studies have demonstrated favorable biocompatibility profiles, the formation of a protein corona on nanomaterials *in vivo* may alter their distribution, reduce targeting precision towards tau aggregates, and trigger immune responses.¹⁰² This underscores the need for

Table 1. Summary of carbon nanomaterial-based theranostic approaches in targeting tau pathology.

Nanomaterials	Representative Properties	BBB Penetration	Detection Limit for Tau	Therapeutic Roles (Mechanistic Highlights)	Diagnostic Roles	Translational Stage / Readiness
Carbon Nanotubes (CNTs)	1D cylinders (SWCNT, MWCNT), high surface area, functionalizable	Moderate (enhanced with targeting ligands)	fM-pg/mL (SPR, electrochemical sensors)	Promote autophagy via mTOR modulation; tau clearance, targeted ACh delivery	SPR, electrochemical, and aptamer-based biosensors for tau and p-tau181	Preclinical (in vitro & in vivo)
Graphene & derivatives (GO, rGO, GQDs)	2D/0D structure, high conductivity and surface area, tunable functionality	Moderate (size- and charge-dependent)	fg-pg/mL (GFET, SERS, ECL, fluorescence sensors)	GQDs inhibit/disaggregate tau fibrils; GO scaffolds deliver methylene blue to reduce tau phosphorylation	Electrochemical, FET, and SERS biosensors for ultrasensitive tau detection	Preclinical (diagnostic near-clinical, therapeutic in vitro)
Fullerenes (e.g., C60, 3HFWC)	Spherical, hydrophobic but functionalizable	Low-Moderate (depends on derivatization)	Not established	Radical scavenging; A β inhibition (implied tau modulation); AChE inhibition, neuroprotection in AD models	Enzyme-free ACh electrochemical sensors (F-HS-Ni)	Early stage (mostly in vitro)
Carbon Nitride Dots (CNDs)	N-rich, tunable polarity, hydrophilic	High (Passive diffusion, zebrafish model)	Not established	ROS scavenging, autophagy induction, tau aggregation inhibition; co-delivery of memantine and siRNA	None reported	Preclinical (in vitro & in vivo)
Carbon Dots (CDs)	<10 nm, hydrophilic, rich in surface functional groups, strong fluorescence	High (CRCD3 – zebrafish model)	Not established	Inhibit tau phosphorylation & aggregation; antioxidant & anti-inflammatory; kinase modulation (GSK-3 β , CDK5)	None reported	Preclinical (in vitro & in vivo)

comprehensive, long-term toxicological and pharmacokinetic profiling in clinically relevant models. Another major challenge concerns the standardization of synthesis and functionalization protocols. Variability in particle size, surface charge, and chemical functional groups can lead to batch-to-batch inconsistencies, impeding reproducibility and comparative evaluation. Moreover, the scalability of carbon nanomaterial production further complicates clinical progression, particularly in ensuring batch consistency and regulatory compliance.

These technical and biological uncertainties are further reflected in recent literature examining the translation readiness of carbon nanomaterials. Teixeira et al.¹⁰³ highlighted that carbon-based nanomaterials, while promising for targeted brain delivery, can induce neuroinflammation, oxidative stress, mitochondrial dysfunction, and glymphatic system impairment. Their review further emphasized that key physicochemical properties—particularly size, surface charge, surface modifications, stiffness, and shape—strongly modulate neurotoxicity in carbon nanostructures, underscoring the need for rigorous nano-neurotoxicological assessment, encompassing *in vitro* and *in vivo* testing, to ensure safe clinical translation. Similarly, Ganguly et al.¹⁰⁴ emphasized that incomplete understanding of absorption, distribution, metabolism, and excretion (ADME) profiles continues to impede regulatory progress. Specifically, graphene derivatives often accumulate in the liver and spleen, CNTs show poor dispersibility and slow clearance, CQDs require neurotoxicity evaluation due to BBB penetration, and fullerenes display surface chemistry-dependent metabolism and elimination. Expanding beyond these scientific barriers, Ma et al.¹⁰⁵ addressed the regulatory dimension, advocating for unified international databases, standardized risk-assessment tools, and adaptive, science-driven frameworks to promote global consistency and safety in nanomaterial regulation.

Adding to these translational hurdles is the heterogeneity of tau pathology across different tauopathies, such as AD, PSP, and frontotemporal dementia, each exhibiting distinct isoform imbalances and deposition patterns.^{106,107} This complexity necessitates the development of nanomaterials engineered to selectively target pathological tau conformers while minimizing off-target effects on normal tau.

Based on our comprehensive analysis, a strategic approach to clinical translation should prioritize three key areas. First, CNDs warrant immediate focus for standardized synthesis development, given their superior BBB penetration and multifunctional capabilities. Second, graphene-based platforms, particularly GQDs, require urgent attention to realize their diagnostic potential and address the current theranostic gap in tau detection. Third, addressing the cytotoxicity concerns of CNTs while harnessing their exceptional drug loading capacity represents a critical bottleneck that, once resolved, could unlock their significant therapeutic potential.

To address these issues, future strategies should prioritize the development of hybrid platforms that combine the

complementary strengths of different carbon nanomaterials—such as integrating the BBB penetration of CNDs with the sensing capabilities of graphene derivatives. A phased clinical translation approach is recommended: immediate focus on diagnostic applications where safety requirements are less stringent, followed by therapeutic applications as long-term safety data becomes available. Leveraging exosome-inspired or exosome-functionalized nanocarriers may offer added benefits by enhancing BBB penetration, reducing immune recognition, and improving targeted payload delivery into the brain.

Ultimately, overcoming these translational hurdles will require robust long-term *in vivo* studies, toxicological profiling, regulatory framework development, and interdisciplinary collaboration to realize the promise of carbon nanomaterials in AD therapy. While significant challenges remain, the unique multifunctional properties of carbon nanomaterials—unmatched by conventional therapeutic approaches—position them as the most viable pathway toward effective tau theranostics. The question is not whether carbon nanomaterials will transform tau-directed therapy, but rather which specific platforms will emerge as clinical leaders and how quickly standardization efforts can accelerate their translation. There is also a compelling opportunity to integrate these platforms into personalized medicine, enabling individualized treatment strategies with real-time monitoring – a frontier where carbon nanomaterials may prove particularly transformative.

Conclusion

Carbon nanomaterials offer a promising theranostic approach to tau-directed therapy, providing integrated solutions that address the targeting, monitoring, and intervention challenges that have limited conventional approaches. The complementary strengths of different carbon nanomaterials, from CNDs' brain penetration capabilities to graphene derivatives' diagnostic potential, position them as attractive candidates for tackling tau pathology's complex requirements. As the field advances from material characterization toward clinical evaluation, carbon nanomaterials represent a significant step forward in developing more sophisticated, multifunctional approaches to tauopathy management.

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