

Nanomaterials-mediated lysosomal regulation: a robust protein-clearance approach for the treatment of Alzheimer's disease

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<https://doi.org/10.4103/NRR.NRR-D-23-01736>

Date of submission: October 22, 2023

Date of decision: January 4, 2024

Date of acceptance: February 20, 2024

Date of web publication: April 3, 2024

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Abstract

Alzheimer's disease is a debilitating, progressive neurodegenerative disorder characterized by the progressive accumulation of abnormal proteins, including amyloid plaques and intracellular tau tangles, primarily within the brain. Lysosomes, crucial intracellular organelles responsible for protein degradation, play a key role in maintaining cellular homeostasis. Some studies have suggested a link between the dysregulation of the lysosomal system and pathogenesis of neurodegenerative diseases, including Alzheimer's disease. Restoring the normal physiological function of lysosomes hold the potential to reduce the pathological burden and improve the symptoms of Alzheimer's disease. Currently, the efficacy of drugs in treating Alzheimer's disease is limited, with major challenges in drug delivery efficiency and targeting. Recently, nanomaterials have gained widespread use in Alzheimer's disease drug research owing to their favorable physical and chemical properties. This review aims to provide a comprehensive overview of recent advances in using nanomaterials (polymeric nanomaterials, nanoemulsions, and carbon-based nanomaterials) to enhance lysosomal function in treating Alzheimer's disease. This review also explores new concepts and potential therapeutic strategies for Alzheimer's disease through the integration of nanomaterials and modulation of lysosomal function. In conclusion, this review emphasizes the potential of nanomaterials in modulating lysosomal function to improve the pathological features of Alzheimer's disease. The application of nanotechnology to the development of Alzheimer's disease drugs brings new ideas and approaches for future treatment of this disease.

Key Words: Alzheimer's disease; autophagy dysfunction; lysosomal acidification; lysosomal system; nanomaterials; neurodegenerative diseases

Introduction

Alzheimer's disease (AD) is the most common form of dementia in older individuals. Currently, the mainstay of AD treatment involves medications that target cholinergic or glutamatergic neurotransmission in the central nervous system. However, it is crucial to note that these treatments only provide symptomatic relief rather than cure. The underlying cause of AD remains unclear; however, it is characterized by the accumulation of amyloid-β (Aβ) plaques and formation of neurofibrillary tangles resulting from tau protein hyperphosphorylation (Twarowski and Herbet, 2023). Lysosomes, responsible for removing abnormal proteins, are believed to play a central role in the development of neurodegenerative disorders such as AD and Parkinson's disease (PD) owing to their impaired lysosomal activity (Van Acker et al., 2019). Recent research has revealed a decline in autophagy function in individuals with AD, occurring even prior to the initial accumulation of Aβ plaques in neuronal cells. Moreover,

studies have shown that the observed Aβ plaques in the brain are the result of neuronal death caused by the accumulation of dysfunctional autophagosomes under conditions of autophagic stress (Lee et al., 2022). These findings provide a novel avenue for pharmacological investigations in the context of AD.

The lysosomal system functions as the primary conduit for the degradation of various biological macromolecules, such as proteins, lipids, nucleic acids, polysaccharides, and other related compounds (Wang et al., 2018; Chen et al., 2022). The cellular composition encompasses a diverse array of hydrolytic enzymes, crucial for upholding the structural integrity of proteins and other macromolecules within the cellular milieu. The system comprises early intranucleosomes, late intranucleosomes, circulating intranucleosomes, and lysosomes (Lai et al., 2021). Under typical circumstances, each of these constituents functions to facilitate the efficient breakdown of macromolecules, particularly proteins. The pathogenesis of AD involves multiple abnormalities in the

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Funding: The work was supported by the Natural Science Foundation of Shanghai, No. 22ZR147750; Science and Technology Innovation Action Plan of Shanghai Science and Technology Commission, No. 23Y11906600; Shanghai Changzheng Hospital Innovative Clinical Research Project, No. 2020YLCYJ-Y02 (all to YY).

How to cite this article: Hao M, Chu J, Zhang T, Yin T, Gu Y, Liang W, Ji W, Zhuang J, Liu Y, Gao J, Yin Y (2025) Nanomaterials-mediated lysosomal regulation: a robust protein-clearance approach for the treatment of Alzheimer's disease. *Neural Regen Res* 20(2):424-439.

lysosomal system, all of which have a dramatic impact on the onset and progression of AD (Whyte et al., 2017; Klein and Hermey, 2023). Consequently, understanding the role of lysosomes in the pathogenesis of AD is essential for therapeutic interventions in AD.

Nanomaterials are entities with dimensions measuring < 100 nm. They find extensive application in the treatment of AD owing to their exceptional surface impact and durability (Bukhari, 2022). A subset of nanomaterials has the ability to selectively aggregate within lysosomes, facilitating the repair of lysosomal damage and restoration of optimal lysosomal pH (Lo and Zeng, 2023). These nanomaterials hold promise in treating AD through their capacity to degrade pathogenic proteins and decrease neuroinflammation, among other potential therapeutic effects (Unnisa et al., 2023). In terms of targeted lysosomal therapy for AD, although certain reviews have explored advancements made in utilizing various small-molecule drugs, to the best of our knowledge, there is currently no all-encompassing and methodical compilation of nanomaterials that targets the lysosomal system, along with a comprehensive review of their classifications and underlying mechanisms of action. Therefore, it is important to provide a comprehensive overview that encompasses advancements and challenges encountered in the field of nanomaterials. This article aims to present a comprehensive analysis of nanomaterials specifically designed to target lysosomes. Various types of nanomaterials have been documented in the scientific literature as potential candidates for targeting lysosomes in the management of AD. These nanomaterials include polymeric nanomaterials, carbon-based nanomaterials, and nanoemulsions (NEs), all of which possess the ability to traverse the blood–brain barrier (BBB) and subsequently restore lysosomal functionality inside cells. In this discourse, we examine the correlation between lysosome-associated damage and the progression of AD and provide an overview of the various circumstances in which lysosomal injury may contribute to the development of the disease. Additionally, we focus on advancements and utilization of nanomaterials that specifically target lysosomes in the treatment and management of neurodegenerative disorders, including AD (**Figure 1**). Furthermore, we propose several approaches for utilizing nanomaterials in the management of AD. These techniques include the removal of pathogenic proteins,

suppression of neuroinflammation, and preservation of neuronal function. In the last section, we discuss the challenges and potential prospects associated with the utilization of lysome-targeted nanomaterials in the management of AD.

Retrieval Strategy

From May 1, 2023 to September 30, 2023, we searched for relevant literature through the PubMed database. Search subject terms included the following: "Alzheimer's disease," "lysosomes," "neurodegenerative diseases," "nanomaterials," "blood–brain barrier," "neuroprotection," and "neuroinflammation." Various combinations of the above search terms were used to comprehensively review the literature. Articles related to AD, lysosomes, and nanomaterials were screened using their titles and abstracts. We also accessed Alzforum (<https://www.alzforum.org/>) to identify ongoing clinical trials on anti-inflammatory treatments for AD.

Alzheimer's Disease and Lysosomal Dysfunctions: Pathogenesis and Therapeutic Interventions

Neurodegenerative maladies are commonly characterized by the accumulation of misfolded proteins and the degeneration of neurons within specific areas of the brain. Autophagy is a cellular mechanism responsible for the destruction of macromolecules within cells. It serves as a crucial channel for the elimination of faulty proteins or organelles, particularly in the nervous system of mammals (Malampati et al., 2020). This process involves the sequestration of proteins and damaged organelles into lysosomes, which rely heavily on the proper functioning of lysosomes (Krishnan et al., 2020; Shojaei et al., 2020a, b). Lysosomes play a vital role as intracellular organelles, containing more than 60 proteolytic enzymes responsible for the degradation of proteins, nucleic acids, and several endogenous and foreign biomolecules (Chen et al., 2022). They are essential for maintaining intracellular protein homeostasis and stability and serve as the primary intracellular digestive compartments. Growing evidence also suggests that lysosomal dysfunction plays a crucial role in the development and progression of AD (Van Acker et al., 2021; Li et al., 2022; Udayar et al., 2022).

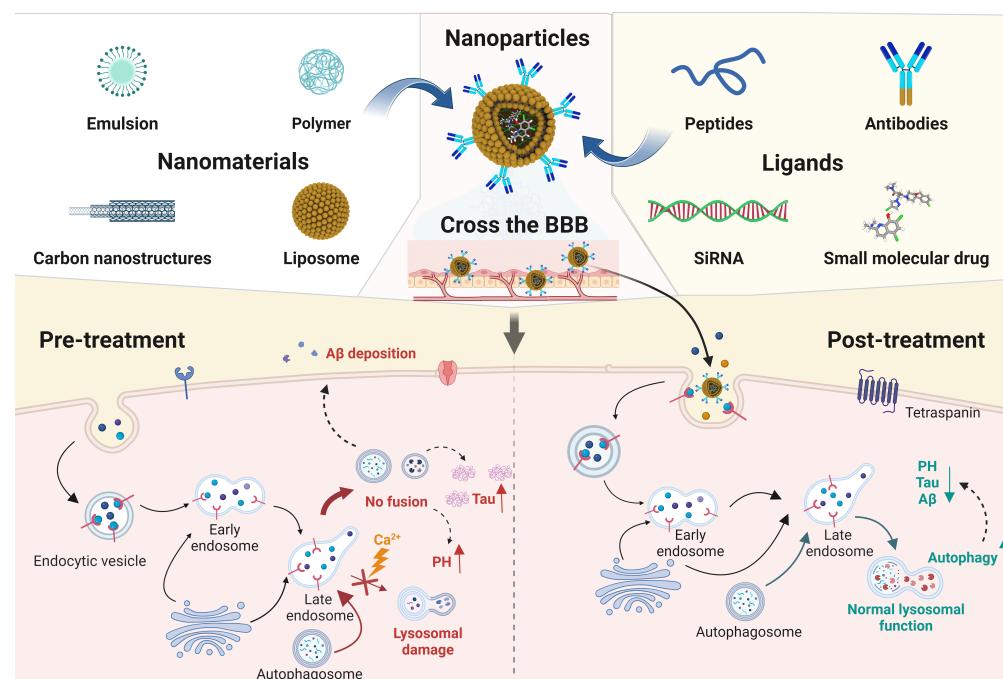


Figure 1 | Nanomaterial synthesis and delivery.

Targeting lysosomes with nanomaterials for the treatment of AD involves treating and injecting nanomaterials into the body to access the AD-affected area of the brain through the BBB. Once inside cells, the nanomaterial reaches the lysosomes, where it restores normal lysosomal function, enhances cellular autophagy, and facilitates the removal of pathological proteins. Created with BioRender.com. AD: Alzheimer's disease; BBB: blood–brain barrier; siRNA: small interfering RNA.

Dysfunction of lysosomes

Lysosomes are acidic organelles that contain several enzymes that hydrolyze and digest macromolecules intracellularly and play critical roles in various cellular functions (Koh et al., 2019; Tian et al., 2022). Lysosomal acidification is crucial for the proper functioning of these enzymes. Regulating the acidity of lysosomes involves the coordinated activity of multiple ion channels, with a particular emphasis on vacuolar ATPase (V-ATP) (Root et al., 2021). This macromolecular complex actively transports protons (H^+) into the lysosome, lowering the pH of the lysosomal lumen to the needed acidic levels. This acidic environment is essential for the activation of numerous hydrolytic enzymes within the lysosome, optimizing their efficiency through pH-dependent mechanisms (Colacurcio and Nixon, 2016). The pH of the lysosomal lumen is maintained within a range of 6.5–4.5, in contrast to the normal cytoplasmic pH, which ranges between 7.2 and 7.4. The ATP-dependent proton pump located on the lysosomal membrane is responsible for maintaining this pH within the lysosomal lumen (Hu et al., 2022). Malfunctioning of the V-ATP complex leads to impaired lysosomal acidification, which affects the function of lysosomal tissue phosphatases (McGuire et al., 2017), resulting in abnormal protein accumulation, severe neuronal complications, lipid oxidation, reactive oxygen species formation (Lee et al., 2010), and impaired substrate digestion, contributing to the development of neurodegenerative diseases. In related studies on AD, it has been proposed that presenilin 1 (PSEN1) knockout mice exhibit reduced expression of the V-ATPase subunit V0a1 and defective V-ATPase enzyme, leading to lysosomal alkalinization and increased Ca^{2+} release (Lee et al., 2010, 2015; Filadi and Pizzo, 2019). Another study showed that in presenilin 1 (PS1) and presenilin 2 (PS2) double knockout cells, reduced Ca^{2+} levels affect lysosome-autophagosome fusion (Coen et al., 2012). Additionally, Mustaly-Kalimi et al. found that dysregulation of intracellular ryanodine receptor- Ca^{2+} homeostasis leads to impaired lysosomal deacidification and protein clearance (Mustaly-Kalimi et al., 2022). These results suggest that Ca^{2+} dysregulation is strongly associated with AD.

Lysosomes contain a diverse range of enzymes that can hydrolyze various protein substrates. However, the effectiveness of these proteases can be compromised by cellular stressors, such as endoplasmic reticulum stress and oxidative stress, leading to impaired lysosomal degradation processes (Colacurcio et al., 2018). Mutations in the cathepsin B (CSTB) gene have the potential to disrupt protein cleavage within lysosomes. Cathepsins are a group of enzymes responsible for protein degradation within lysosomes. Abnormalities in the CSTB gene result in excessive secretion of cystatin B, which inhibits cathepsin activity and impairs the hydrolytic clearance of proteins within lysosomes. This results in a significant accumulation of A β within lysosomes, leading to the buildup of intralysosomal A β and the deposition of A β extracellularly (Yang et al., 2011; Lai et al., 2021). The CSTB gene is responsible for storing cystatin B, a lysosomal cysteine protease inhibitor, along with cathepsin. This impairs lysosomal function and contributes to the development of AD. In accordance with the requirements of the β -site amyloid- β A4 precursor protein-cleaving enzyme 1 (BACE1) locus, lysosomes contain enzymes that regulate or promote the amyloidogenic process, such as membrane type 1 matrix metalloproteinase (Van Acker et al., 2021). Membrane type 1 matrix metalloproteinase is located upstream of the BACE1 locus and accelerates the cleavage of BACE1 and promotes amyloidogenic protein production (Liao and Van Nostrand, 2010). Thus, lysosomal enzymes play an instrumental role in the pathogenesis of amyloidosis.

Lysosomes and the production of A β

A β deposition entails a core part of AD pathophysiology. Research has indicated that the formation of A β is a result of the cleavage of amyloid precursor protein (APP) by certain enzymes. The split of neurons, neurogenesis, synaptic function, apoptosis, and cell proliferation are among multiple events in which APP is implicated (Milosch et al., 2014; Fanutza et al., 2015; Cho et al., 2022). Similar to other functional proteins in the human body, APP undergoes a swift synthesis cycle within the endoplasmic reticulum. Upon synthesis, APP promptly encounters conveyance to the Golgi apparatus, a cellular organelle responsible for its encapsulation into vesicles. The synthesized APP follows two separate processing pathways, namely, the non-amyloidogenic pathway and the amyloidogenic pathway (Wang et al., 2017). In the amyloidosis pathway, APP undergoes initial cleavage by β -secretase (also known as BACE1), leading to the formation of a type of APP β -C-terminal fragment (APP- β CTF). This intermediate byproduct is further cleaved by γ -secretase, leading to an increase in A β levels (Salminen et al., 2013). A study revealed that APP- β CTF can pathologically activate Rab5 by binding to the adaptor protein containing the pleckstrin homology domain, phosphotyrosine binding domain, and leucine zipper motif (APPL1) on early endosomes (Colacurcio et al., 2018). Rab5 is pathologically activated in the amyloidogenic pathway, promoting the early endosomal processing of APP and leading to increased A β production, which may contribute to AD.

Furthermore, deletion of the sortilin-related receptor 1 (SORL1) gene has been shown to impair lysosomal function. The SORL1 gene encodes regulators involved in protein transport between the trans-Golgi network and endosomes, including APP (Andersen et al., 2016). When the SORL1 gene is absent, neuronal lysosomal CTSD activity is significantly reduced, lysosomal clearance is impaired, autophagic vesicles accumulate, and APP is translocated to regions of endocytosis that are favorable for A β production, leading to increased A β production (Dodson et al., 2008; Hung and Livesey, 2021; Hung et al., 2021). This also reduces the degradation of A β in lysosomes, further exacerbating A β accumulation (Caglayan et al., 2014). In one additional study, Sannerud et al. (2016) proposed that PSEN2/ γ -secretase, which is mainly restricted to late endosomes/lysosomes, is important for the establishment of intracellular A β pools and that the familial AD-presenilin 2 (FAD-PSEN2) mutation significantly increases the ratio of intracellular A $\beta_{42/40}$, revealing an important role of specific intracellular localized responses in the pathogenesis of AD. Mutations in the APP gene (chr21) are also a genetic feature of AD (Li et al., 2021). There are over 50 highly pervasive synapses in chr21, which make APP more susceptible to cleavage to produce the neurotoxic A β_{1-42} , accelerating the progression of AD (Cacace et al., 2016). Moreover, reduced APP protein alleviates neuronal endolysosomal dysfunction caused by SORL1 deficiency, suggesting that APP also plays a role in regulating the endolysosomal system (Hung et al., 2021). The A β theory is widely recognized in the pathogenesis of AD, and an understanding of A β production is crucial for the development of therapeutic approaches for AD (Selkoe and Hardy, 2016).

Lysosomes and the accumulation of tau

Tau proteins and their aggregated forms are also substrates for lysosomal degradation (Politio et al., 2014), and impaired lysosomal function may contribute to the accumulation of misfolded/aggregated tau (Xu et al., 2021). It has been suggested that lysosomal dysfunction may accelerate the accumulation of tau proteins in AD by triggering the release of lysosomal calcium, which in turn promotes pathological changes in tau proteins (Rao

et al., 2014), leading to the formation of neurofibrillary tangles. Furthermore, lysosome biogenesis is regulated by transcription factor EB (TFEB) (Xue et al., 2023). Recent evidence suggests that TFEB can facilitate the clearance of pathogenic proteins associated with AD by regulating the cytoplasmic distribution and nuclear translocation of lysosomes (Li et al., 2022). Notably, the retromer is also critical for maintaining lysosomal function and tau protein clearance. The retromer is a multimodular protein assembly, and the vacuolar protein sorting-associated protein 35 (VPS35) is the backbone molecule of the retrotransporter complex and the scaffold for all other retrotransporter complex modules and receptor binding (Small and Petsko, 2015). It has been shown that lysosomal degradation is reduced in VPS35 knockout HeLa cells, and lysosomal targeting and *in vitro* activity of β-galactosidase are decreased (Cui et al., 2019). Autophagic flux is notably reduced in VPS35-deficient cells, which may be due to impaired lysosomal protein hydrolysis and increased microtubule-associated protein tau (MAPT)/tau aggregation (Carosi et al., 2021). In addition, TFEB can also remove the MAPT through autophagy/lysosomal system remodeling and chaperone-mediated autophagy (Binder et al., 2020; Gorantla and Chinnathambi, 2021). In addition to the above-mentioned tau-related species, APP is also closely associated with tau pathology in AD (Dave et al., 2023). Increased APP leads to tau mislocalization, and the accumulation of mislocalized tau proteins forms protofibrillar seeds and multiplies, resulting in a vicious cycle of accumulation of tau proteins, which suggests that excess APP in the AD brain is correlated with tau pathology in AD (Kametani and Hasegawa, 2018; Dave et al., 2023).

One potential therapeutic approach for AD involves strategies to restore or enhance lysosomal function. However, the efficacy of current drugs may be limited by the BBB and the lack of specific targeting capabilities. Nanodosing enables site-specific delivery, improved drug solubility (Hettiarachchi et al., 2019), and enhanced therapeutic efficacy by targeting lysosomes.

Nanomaterials Targeting Lysosomal Strategies

Nanomaterials have created a new wave in the medical field, offering new hope to patients with AD and others suffering from challenging diseases. Their distinct characteristics (e.g., small size and high targeting) make them the preferred recipients of target-drug delivery for precise treatment of diseased areas of the brain. In this section, we outline current strategies for nanomaterial targeting of lysosomes.

Nanomaterials that modify lysosomal fiber have inspiring potent utility in the investigation and cure of debilitating neural degenerative disorders. Depending on the carrier material, nano-drug delivery systems can be broadly classified into two categories: organic and inorganic, and nanomaterials are linked to biomolecules or ligands for specific targeting (Figure 2; Karthivashan et al., 2018; Gupta et al., 2019). In this summary, we focus on the development of nanomaterials that target lysosomes for the treatment of AD. Table 1 provides an overview of the application of different nanomaterials in AD.

Nanomaterials and BBB

The BBB serves as a crucial protective layer in the brain, acting as both a metabolic and transport barrier to shield it from potentially hazardous signals. The framework encompasses brain capillary endothelial cells and neuroglial cells that are interconnected via tight junctions. Endothelial cells are bound by a basolateral membrane capped by the end-foot of glial astrocytes and are subject to continuous monitoring by microglia (Zenaro et al., 2017; Zhao et al., 2021). This results in limited paracellular transport, allowing the passage of only small hydrophilic molecules and ions. Additionally, the transportation pathway for lipids is confirmed (Sánchez-Navarro et al., 2017). Multiple infrastructures, notably carrier-mediated transcytosis, receptor-mediated transport, cell-mediated endocytosis, and adsorptive transcytosis, facilitate the transportation of vital components to the brain through particular channels (Chen and Liu, 2012; Gao, 2016). The BBB poses a significant obstacle to the effective management of AD. The efficacy of AD would necessitate the transportation of the therapeutic agent across the BBB, which prohibits approximately 98% of upcoming neuropharmaceuticals from penetrating the brain (Gregori et al., 2015; Yin et al., 2023a). In contrast, nanomaterials can tackle this dilemma by effectively penetrating or bypassing the BBB, facilitating drug delivery to the brain through appropriate modifications, and boosting the efficiency and stability of drug delivery (Chu et al., 2022; Woon et al., 2022; Anwar et al., 2023; Figure 3).

Polymeric nanoparticles

The retention of both organic and synthetic polymeric nanomaterials is feasible. Polymeric nanomaterials can be chemically synthesized through emulsification, salt precipitation, and nanoprecipitation (Masood, 2016). Polymeric nanomaterials exhibit high drug-loading capacity and show minimal toxicity.

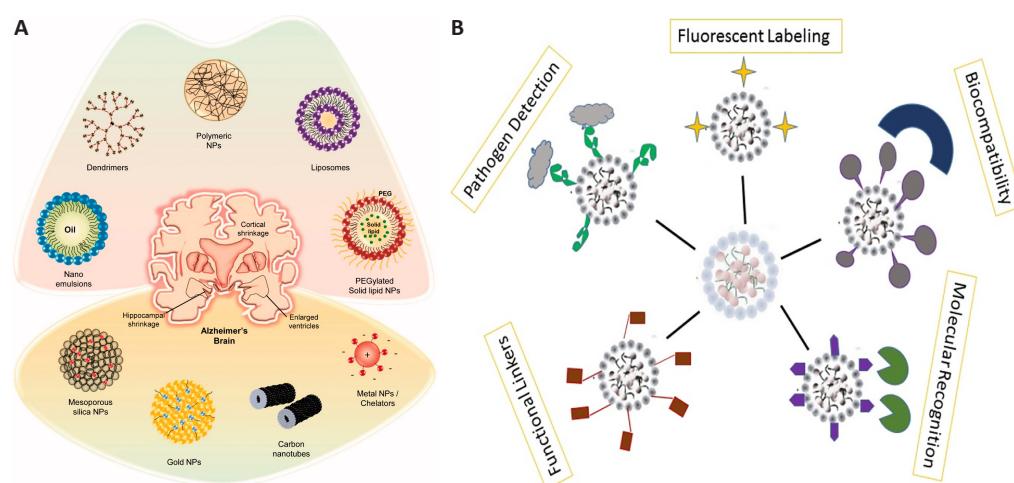


Figure 2 | Nanomaterials for treating AD.

(A) Various effective nanotherapeutic nanomaterials for AD. Reproduced with permission from Karthivashan et al. (2018). (B) Various methods for nanomaterial synthesis. Reproduced with permission from Gupta et al. (2019), Copyright 2019 Elsevier B.V. All rights reserved. AD: Alzheimer's disease; NP: nanoparticle.

Table 1 | Application of nanomaterials in AD therapy

Sort	Size (nm)	Framework	Feature	Efficacy for AD	Route of administration/ model system	Translational/ clinical trial	Transparent BBB	Reference
Liposomal NPs	25–10000	Spherical structure, phospholipid bilayer	Nontoxic, nonimmunogenic, easy to target	A β clearance, acetylcholine lipase inhibition	Intravenous injection/Sprague-Dawley rats, bEnd.3 cells, primary rat glia, primary rat neuronal cells	WO 2014 076709A1	Conjugated to cell-penetrating peptides such as TAT, pVec, and QL	Agrawal et al., 2017; Dos Santos Rodrigues et al., 2019
Polymer NPs	10–300	Multiple configurations	Excellent biocompatibility and biodegradability	Immunomodulatory, antioxidant, anti-inflammatory	Intranasal delivery/16HBE cells, SH-SY5Y cells	/	Coupled Lf	Ouyang et al., 2017; Meng et al., 2018; Aliev et al., 2019
Carbon-based NPs	1–1000	Polyhedral carbon structure, physical, and seamless tubular structure	Superior chemical, physical, and electronic properties	Antioxidant, neuroprotective, scavenging A β	Intravenous injection/SH-SY5Y cells, Wistar rats	/	Receptor-mediated pathway	Lohan et al., 2017; Mohajeri et al., 2019; Elsori et al., 2023
Nanoemulsion	50–1000	Orbicular	Nontoxic, nonirritating, highly biocompatible	Dose-dependent cytotoxicity, antioxidant activity	Intravenous injection/BE (2)-M17 (human neuroblastoma)	267/KOLNP/2007	Combined with NLs	Cunha et al., 2020; Agrawal et al., 2021; Ansari et al., 2023

AD: Alzheimer's disease; A β : amyloid- β ; BBB: blood-brain barrier; Lf: lactoferrin; NL: nucleolipid; NP: nanoparticle; pVec: vascular endothelial-cadherin-derived peptide; QL: hydrophobic pentapeptide QLPVM; TAT: trans-activator of transcription.

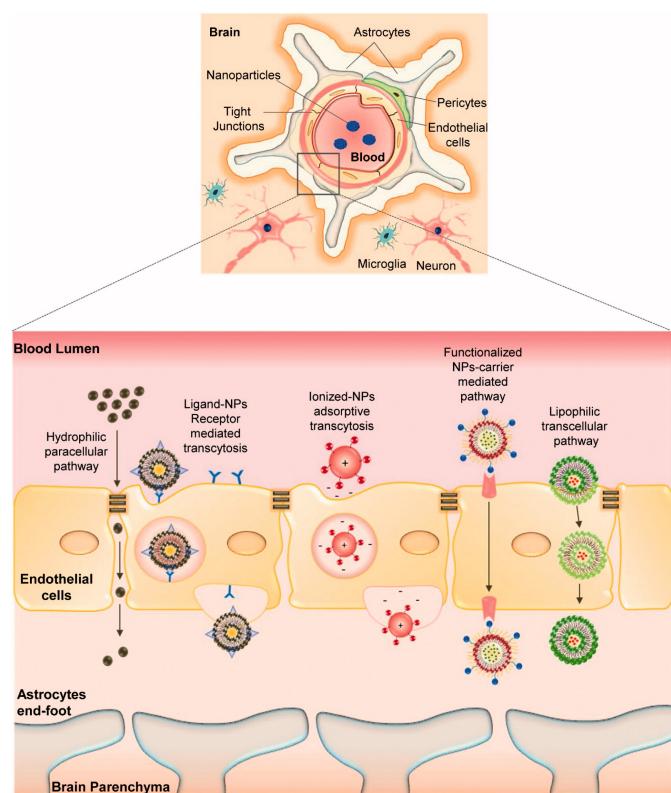


Figure 3 | Nanomaterials transportation pathways.

The schema of the pathways involved in the transportation of nanomaterials across the blood-brain barrier. Reproduced with permission from Karthivashan et al. (2018). NPs: Nanoparticles.

Notably, toxicity can be reduced by polyethylene glycol (PEG)-phospholipid copolymers (Hettiarachchi et al., 2019). Polyhydroxylalkanes, polylactide-co-glycolide (PLGA), cyclodextrin-derived, and PEG-coated polymeric nanomaterials are widely used in brain research as nanoscale carriers. In the context of

AD therapy, PLGA and PEGylated polymeric nanomaterials are commonly encountered (Masood, 2016). PLGA is a synthetic hydrophobic polyester composed of monomers derived from lactic acid and glycolic acid. These monomers can be assembled randomly or as block copolymers. The legalization of PLGA by the U.S. Food and Drug Administration may be credited to its extraordinary biocompatibility, biodegradable properties, biosafety, and adaptability, making it one of the finest polymers in the field of biomedicine (Martins et al., 2018). PLGA micro/nanomaterials have been utilized as drug delivery systems for a wide range of small molecules. These molecules include pharmaceuticals, physiologically active compounds, and therapeutically relevant molecules to assist in the management of various diseases (Rezvantalab et al., 2018; Essa et al., 2020).

Bourdenx et al. (2016) provided evidence that PLGA-based nanomaterials can induce changes in lysosomal function in multiple cellular models of PD, including toxic and genetic models. The cellular uptake of the nanomaterials and their subsequent targeting of lysosomes have been thoroughly investigated. In Bourdenx's study (Bourdenx et al., 2016), fibroblasts derived from patients with PD carrying a lysosome-related transmembrane P5-type ATP transportase (ATP13A2) mutation were treated with PLGA-based nanomaterials, and a comparison was made with normal human fibroblasts. The results demonstrated that treatment with PLGA-based nanomaterials successfully restored lysosomal pH to normal levels (Figure 4A). Immunoblotting revealed a decrease in the accumulation of microtubule-associated protein 1 light chain 3 β -II, which significantly enhanced the clearance of autophagosomes (Figure 4B). Functional assays confirmed the restoration of lysosomal proteolytic activity in PLGA-based nanomaterial-treated fibroblasts compared to untreated fibroblasts (Figure 4C). Additionally, the breakdown products of PLGA, consisting of lactic and glycolic acids, have the ability to modulate lysosomal pH levels (Cunha et al., 2021a). Although the primary focus of the publication is on PD, the researchers also provided evidence that PLGA-based nanomaterials can exert their effects in other clinical conditions. A recent study by Wu et al. (2022), revealed that the use of

plain PLGA without any drugs or agents had inhibitory effects on both A β aggregation and toxicity. Wu et al. (2022) utilized primary mouse cortical neurons to demonstrate that plain PLGA is internalized through an energy-mediated clathrin-dependent/independent pathway and accumulates within endosomal-lysosomal-autophagic vesicles. Moreover, the study by Paul et al. (2022) provided evidence that PLGA nanomaterials can inhibit A β aggregation and induce the disintegration of A β aggregates even at nonphysiological temperatures. These nanomaterials have also been shown to protect neurons against the detrimental effects of A β -induced toxicity. These findings validate the unique therapeutic capabilities of PLGA nanomaterials in combating the pathological mechanisms associated with dementia (**Figure 4D**). PLGA without conjugation inhibits spontaneous aggregation and promotes disassembly at various temperatures (27–40°C) (**Figure 4E**). Additionally, Wang et al. (2020) reported that PLGA protects primary cortical neurons from A β toxicity over time by attenuating lysosomal membrane permeability. Furthermore, the protective effect of PLGA against A β -induced toxicity was accompanied by reduced activation of extracellular-signal related kinase 1/2 and glycogen synthase kinase (**Figure 4F** and **G**) and decreased levels of phosphorylated and cleaved tau protein as well as cleaved caspase-3 (**Figure 4H**; Wang et al., 2020). In another study, Govindarajan and Kar (Govindarajan and Kar, 2023)

confirmed that PLGA can recognize A β and neurotic plaques in AD mice, demonstrating the potential of PLGA for the treatment and diagnosis of AD. Extensive research has been conducted in the past decade to explore the use of PLGA nanomaterials as innovative therapeutic approaches for various neurodegenerative disorders, including AD. The available results thus far indicate that drug-loaded PLGA nanomaterials may have potential in the treatment of neurodegenerative diseases. However, despite the approval of PLGA by the U.S. Food and Drug Administration as a drug-controlled release carrier, there is currently no clinical application of PLGA in the management of neurodegenerative diseases; hence, further research is still needed.

PLGA is widely used in the study of AD therapeutics due to its high biocompatibility, low toxicity, good tissue permeability, and targeting properties (Ege, 2021). However, PLGA nanomaterials still have some drawbacks and limitations. Although reports show that small-sized PLGA can cross the BBB, the efficiency of the drug reaching pathological regions of the brain is still low (Huang et al., 2017). Additionally, the high production cost of PLGA is not conducive to drug development and commercialization (Rocha et al., 2022). Further comprehensive investigations are needed to maximize the clinical efficacy of PLGA nanomaterials in the therapeutic management of AD.

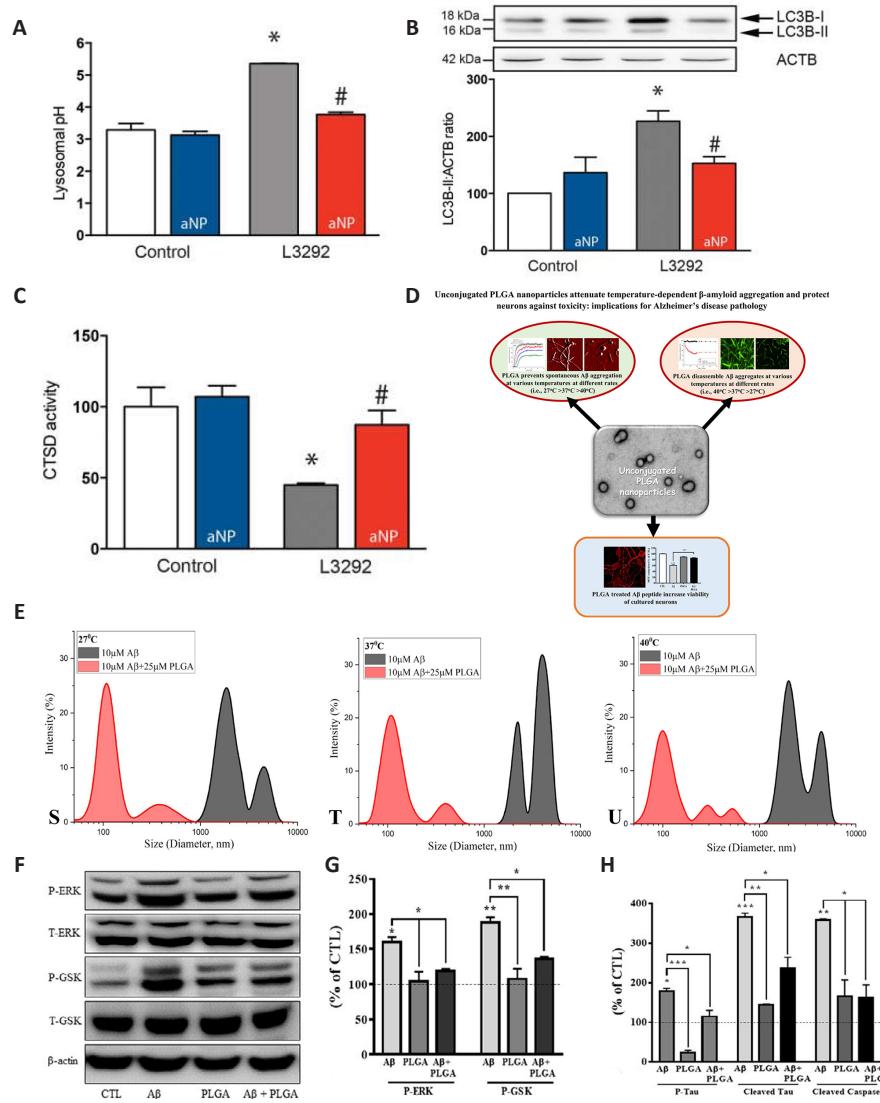
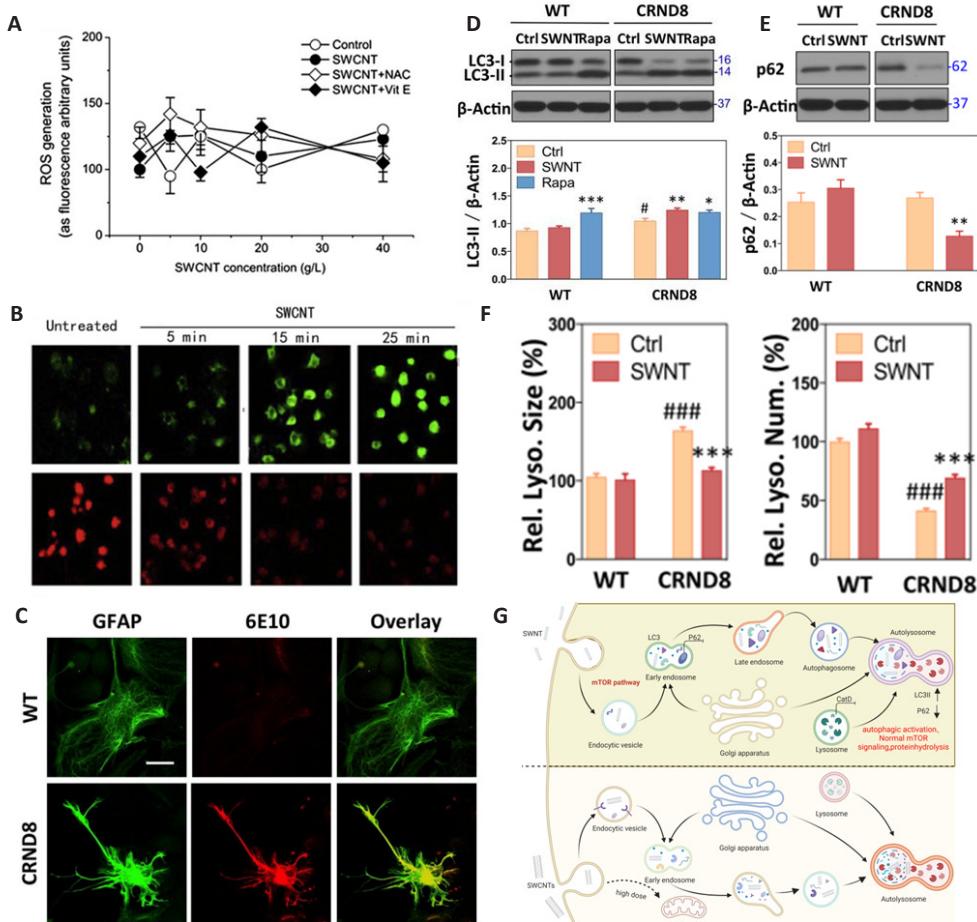


Figure 4 | Polymeric nanomaterials revive lysosomal fibers.

(A) Regular and recombinant ATP13A2 L3292 stromal lysosomal pH alone or via PLGA-aNPs were measured. (B) Altered ATP13A2 L3292 oocytes with or without PLGA-aNPs were analyzed using immunoblotting. (C) Probing the functioning of CTSD in normal and defective ATP13A2 stromal lysosomes. *P < 0.05, vs. control untreated cells; #P < 0.05, vs. L3292 untreated cells. A–C were reproduced with permission from Bourdenx et al. (2016), Copyright 2016 Taylor & Francis. (D) Temperature-dependent A β aggregation was attenuated using unconjugated PLGA. (E) Dynamic light scattering analysis was performed on aggregated A β_{1-42} populations after 72 hours of incubation at 27°C, 37°C, and 40°C, with and without 25 μ M PLGA. D and E were reproduced with permission from Paul et al. (2022). (F, G) Phosphorylated ERK1/2 and GSK-3 β levels induced by A β_{1-42} were attenuated using 200 μ g/ml PLGA treatment. (H) Caspase-3, phospho-tau, and cleaved tau levels were increased. *P < 0.05, **P < 0.01. F–H were reproduced with permission from Wang et al. (2020), Copyright 2020 John Wiley and Sons. ACTB: β -Actin; aNP: acidic nanoparticle; ATP13A2: ATPase type 13A2; A β : amyloid- β ; CTL: control; CTSD: cathepsins D; ERK1/2: extracellular-signal related kinase 1/2; GSK-3 β : glycogen synthase kinase; LC3B: microtubule associated protein 1 light chain 3 β ; P-ERK: phospho-Thr202/Tyr204 extracellular-signal related kinase 1/2; P-GSK: GSK-3 β : phospho-Tyr216 glycogen synthase kinase; PLGA: poly(DL-lactide-co-glycolide); T-ERK: total extracellular-signal related kinase 1/2; T-GSK: total glycogen synthase kinase.

Carbon-based nanoparticles

Carbon-based nanomaterials exist in various forms, including carbon nanotubes, fullerenes, graphene, and carbon dots. Among them, carbon nanotubes and carbon dots are commonly used as adsorbents in adsorption investigations (Augustine et al., 2017). Carbon nanotubes are characterized by long cylindrical hollow structures and can be categorized as single-walled nanotubes (SWCNTs) or multi-walled nanotubes based on the number of graphene sheets they contain. The excellent physical properties of carbon nanotubes have led to a wide range of applications for *in vivo* drug delivery. Yang et al. (2010) conducted a study to evaluate the pharmacological and toxicological characteristics of SWCNTs for drug delivery purposes. Cytotoxicity research on SWCNTs has shown that, compared to lysosomes, the mitochondria produce more reactive oxygen species (Figure 5A). The presence of SWCNTs led to a significant reduction in the loss of mitochondrial membrane potential observed through confocal laser scanning microscopy using JC-1 fluorescent dye (Figure 5B). These results suggest that mitochondria are the target organelles for SWCNT toxicity. Yang et al. (2010) also found that SWCNT dosages below 300 mg/kg could reduce mitochondrial cytotoxicity. By carefully controlling the dosage and considering the specific dosage requirements for different organelles, the prioritized uptake of SWCNTs by lysosomes can be achieved. This would facilitate the effective delivery of acetylcholine to the brain while maintaining safety parameters for the treatment of AD in experimental models. In another study, Xue et al. (2014) investigated the autophagy capabilities of CRND8 animals and wild-type controls, as well as the impact of single-walled carbon nanotubes (SWNT) therapy on autophagy competence in isolated



primary glial cells (Figure 5C). The researchers performed immunoblot analyses using various autophagy pathway markers to assess different stages of the autophagy pathway. These stages included evaluating the mechanistic target of rapamycin (mTOR) activation state, autophagosome formation through LC3-positive vesicle identification, lysosomal functionality by examining LC3 and p62 turnover, cathepsin D maturation, and lysosome acidification (Figure 5D–F). The findings of the study suggested that functionalized SWNTs can effectively restore proper autophagy function by reversing abnormal mTOR signaling and correcting deficiencies in lysosomal proteolysis. This also facilitates the elimination of autophagic substrates (Figure 5G). Although the mechanism by which SWNT improves autophagy still requires further study, these results provide conceptual evidence for nanoparticle (NP) therapy for autophagy injury.

Carbon-based nanomaterials possess excellent electrical, mechanical, and chemical properties, making them valuable in the medical field. Numerous studies have demonstrated the therapeutic potential of carbon-based nanomaterials in the treatment of brain disorders (Du et al., 2018; Wang et al., 2019; Chu et al., 2021; Yin et al., 2023b). However, their production cost is high, and they are difficult to produce on a large scale; hence, further research is needed.

NEs

NEs are gelatinous dispersions composed of two immiscible fluids stabilized by surfactants. The droplets in NEs exhibit a wide range of sizes, from 20 to 500 nm (Figure 6A; Liao et al., 2018; Karami et al., 2019). NEs can be classified into different types, such as

Figure 5 | Carbon-based nanomaterials for AD.

(A) SWCNTs' effects on lysosome ROS production. (B) SWCNTs enhance green fluorescence and reduce red fluorescence over the course of incubation, indicating the modification of MMP. A and B were reproduced with permission from Yang et al. (2010), Copyright 2010 Elsevier Inc. All rights reserved. (C) 6E10 antigen (red) and glial GFAP (green) immunofluorescence in WT and CRND8 glial cells. (D, E) Western blot analysis demonstrating LC3 and p62 expression. (F) Size and number of lysosomes. * $P < 0.05$, ** $P < 0.01$, vs. Ctrl; # $P < 0.05$, vs. WT. C–F were reproduced with permission from Xue et al. (2014), Copyright 2014 American Chemical Society. (G) Carbon-based NPs for the treatment of AD. Created by BioRender.com. AD: Alzheimer's disease; Ctrl: control; GFAP: glial fibrillary acidic protein; LC3: microtubule-associated protein 1 light chain 3; MMP: mitochondrial membrane potential; Rel.: relative; ROS: reactive oxygen species; SWCNT: single-walled carbon nanotube; WT: wild type.

water-in-oil (W/O), oil-in-water (O/W), and water-in-oil-in-water (W/O/W), depending on the composition of the materials and the arrangement of the internal and external phases. The phase-to-volume ratio (Φ) plays a crucial role in determining the quantity of NE droplets and the observed instabilities in the system. Φ represents the relative volumes of the inner and outer liquids, which have different properties.

NEs offer better kinetic stability than other nanomaterials due to their small size, where Brownian motion dominates the gravitational force. Among the various types of NEs, O/W NEs are most commonly used for treating neurodegenerative conditions in the brain. Brouillard et al. (2021) developed lipid-based nucleic acid nanomaterials using O/W NEs. Nucleolipids (NLs) are organic compounds composed of a lipid molecule covalently bonded to a precursor of an amino acid, such as a nucleobase, nucleoside, nucleotide, or oligonucleotide. In the study, two novel inorganic compounds (compounds 7 and 8) with a succinate group at the 5' position and palmitate and arachidonate at the 3' position (**Figure 6B**; Brouillard et al., 2021) were designed, synthesized, and evaluated biologically as lysosomal pH agonists (Brouillard et al., 2021). Experimental results showed that nucleic acid-lipid-

based nanomaterials are effective at lowering the lysosomal pH and restoring the function of lysosomes. Subsequently, the authors undertook a deeper investigation and synthesized the tetramer NL (Brouillard et al., 2023). Biological evaluation showed that tetramer NL releases succinic acid and restores the optimal lysosomal pH. The active concentration of tetramer NL was reduced by a factor of four compared to the corresponding monomer. In a separate experiment, Geoffrey prepared an oil-in-water NE with PLGA encapsulated inside the NE (**Figure 6C**; Prévot et al., 2018). Using this approach, the concentration of fluorescent PLGA within the nanomaterial increased from 0.18 to 0.56 g/L (Bourdenx et al., 2016). The laboratory results demonstrated the ability of NE-PLGA to cross the BBB, penetrate brain tissue, and ultimately localize within lysosomes in the brain (**Figure 6D**). Similarly, NE-PLGA could restore acidic pH levels within cellular lysosomes (**Figure 6E**). **Table 2** provides examples of NE delivery to the brain.

The application of NEs has shown promise in the reacidification of lysosomes that have undergone acidification, thereby facilitating the restoration of normal lysosomal function. This approach holds potential for the management of AD. However, it is worth

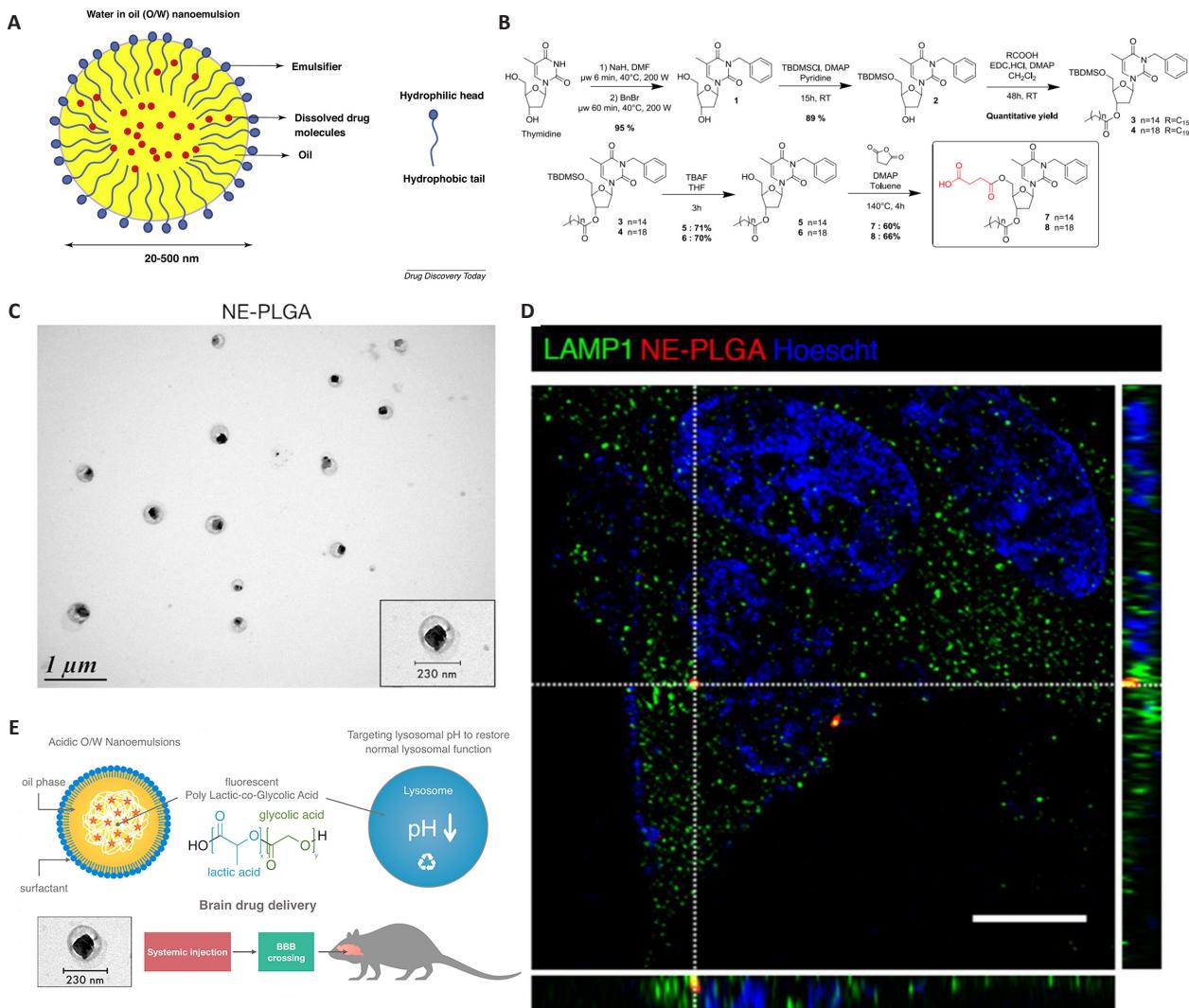


Figure 6 | Nanoemulsions govern lysosomal pH.

(A) Nanoemulsion system with oil-in-water. A was reproduced with permission from Karami et al. (2019), Copyright 2019 Elsevier Ltd. All rights reserved. (B) A synthetic pathway for nucleolipids 7–8. B was reproduced with permission from Brouillard et al. (2021). All rights reserved. (C) Acidic nanoemulsions imaged using TEM. (D) Colocalized immunofluorescence Z-stacks orthogonally projected. (E) PLGA salvages lysosomal pH. C–E were reproduced with permission from Prévot et al. (2018), Copyright 2018 American Chemical Society. LAMP1: Lysosomal associated membrane protein 1; NE: nanoemulsion; PLGA: polylactide-co-glycolide; RT: room temperature; TEM: transmission electron microscope.

Table 2 | Overview of nanoemulsions in central nervous system diseases

Drug	Size (nm)	Drug effect	Outcome	Reference
Risperidone	15.5–16.7	Antipsychotic	Reduced drug side effects, dosage, and frequency of administration	Kumar et al., 2008b
Olanzapine	20.1–23.6	Schizophrenia medication	Reduced dosage and frequency of administration to maximize therapeutic indices	Kumar et al., 2008a
Ergoloid mesylate submicron emulsions	108.5±34.3	Antioxidation	Improve drug absorption and reduce toxicity	Yu et al., 2009
Nimodipine	40–300	Anti-dementia and cerebral vasospasm	Reduced drug efflux and clearance, prolonged extended release of drug	Pathak et al., 2014
Chloramphenicol	100.12±4.35	Anti-inflammatory	Improved solubility and targeting of drugs	Musa et al., 2013
Kaempferol	3.08±17.33	Anti-inflammatory, antioxidant, antibacterial	Improved drug-loading capacity and encapsulation efficiency	Colombo et al., 2017
Zolmitriptan	42.93±1.53	Suppresses vasodilation and inflammation	Improved drug delivery efficiency, bioavailability, and therapeutic efficacy	Abdou et al., 2017
Quetiapine	144±0.5	Antipsychotic drug	Increased drug solubility and bioavailability	Boche and Pokharkar, 2017
Paroxetine	58.47±3.02	Antidepressant and anti-anxiety	Increased drug availability in biology, with a 2.57-fold increase in drug delivery rate	Pandey et al., 2016
curcumin	14.4–118.9	Suppresses Aβ sedimentation and inflammation	Increased drug release and penetration	Sood et al., 2014
Resveratrol	102±1.46	Mitigation of oxidizing stress	Increased drug concentration and targeting efficiency in the brain	Pangeni et al., 2014
Selegiline	10.0±203.0	Neuroprotective and antioxidant	Increased drug penetration and improved behavioral activity in PD mice	Kumar et al., 2016

Aβ: Amyloid-β; PD: Parkinson's disease.

noting that NEs may exhibit insufficient equilibrium, leading to drug leakage during storage, which can impact the overall effectiveness of drug delivery mediated by NEs.

There are two main aspects of targeting lysosomes. One is the direct targeting of drugs to lysosomes or receptors on the surface of endosomes, such as folate, vascular endothelial growth factor, LDL, and transferrin, through receptor-mediated endocytosis (Gopalan et al., 2020). Glucose cerebrosidase is present in lysosomes and is involved in sphingolipid degradation. Some researchers extracted a recombinant enzyme and modified it to expose mannose residues, and after being injected into the body, receptor-mediated endocytosis successfully transported the enzyme into lysosomes (Sly and Vogler, 2002).

Furthermore, endosomal escape is required to ensure that the drug escapes the lysosome, preventing degradation and maintaining the integrity of the drug for better efficacy (Sakhrani and Padh, 2013). Current therapeutic agents targeting lysosomal dysfunction are mainly small-molecule drugs (e.g., small molecules that activate V-ATPase function, regulate TFEB expression, and inhibit mTOR signaling) and nanomedicines (Quick et al., 2023). A study has shown that C381 can target lysosomes and stimulate lysosomal acidification, attenuate lysosomal membrane permeability, and increase proteolysis (Vest et al., 2022). Importantly, C381 has been shown to permeate the BBB and is a potential drug of choice for restoring lysosomal function in the treatment of neurodegenerative diseases (Vest et al., 2022). Additionally, EN6 is a promising small-molecule drug that inhibits the mammalian target of rapamycin complex 1 (mTORC1), stimulates lysosomal acidification, induces autophagy, and enhances cell clearance (Chung et al., 2019). However, EN6 has other off-targets that may trigger other biological effects (Chung et al., 2019). In addition to small-molecule drugs, researchers have developed nanodrugs that target lysosomes. These nanodrugs can be localized into the lysosome to restore the normal pH of the lysosome (Brouillard et al., 2021). Nanomedicines are increasingly used in the treatment of neurodegenerative diseases due to their superior properties,

but there are considerable challenges. The first is the efficiency of penetrating the BBB, and optimizing the chemical formulation or incorporating BBB-penetrating peptides is crucial for nanomedicine brain targeting (Huang et al., 2017). The second is the consistency of nanomedicine size and dispersion, which is related to the clinical translation of nanomedicine as well as drug distribution and reproducibility in accordance with the Good Manufacturing Practices quality standard of drugs.

Downstream Changes in Targeted Lysosomal Therapy

Pathological protein clearance

Pathological characteristics associated with AD involve the accumulation and persistence of Aβ and tau peptides. The deposition of these two proteins plays a crucial role in the progression of AD. Therefore, targeting the removal of pathogenic proteins through scavenging mechanisms holds potential as a therapeutic approach for AD (Yuyama et al., 2015). Viswanathan et al. (2012) investigated the inhibitory effect of Z-Phe-Ala-diazomethylketone on cathepsins B and L and found that it can modestly inhibit these enzymes, leading to increased lysosomal cathepsin levels at low concentrations. Nonpeptidic compounds SD1002 and SD1003 were evaluated as irreversible inhibitors of cathepsin B derived from Z-Phe-Ala-diazomethylketone. These compounds were found to be effective lysosomal modulators, inducing a protective scavenging response against paired helical filaments τ and Aβ₄₂ in various brain regions, including the hippocampus. Similar effects were observed with resveratrol (R), which was found to reduce the accumulation of Aβ and plaque formation, exerting a beneficial impact on an AD model (Vingtdeux et al., 2008). Cathepsin and other lysosomal enzymes may be involved in Aβ degradation in the presence of resveratrol. Nanomaterials have the potential to act as lysosomal modulatory agents in the amelioration of AD.

Autophagy-defective lysosomal dysfunction has been postulated to be closely related to Aβ deposition. The protein kinase mTOR regulates the activation of macromolecular

complexes that collaborate with subcellular membranes to form autophagosomes, which encapsulate cytoplasmic components for degradation in lysosomes. Dysfunctional mTOR signaling leads to poor autophagy induction and protein accumulation. Xue et al. (2014) proposed the administration of SWNT as a potential remedy for AD-associated amyloidosis in a transgenic mouse model (CRND8). The findings indicate that SWNT can effectively rectify two dysfunctions related to autophagy: reversing poor autophagy induction caused by aberrant mTOR signaling and reversing impairment of lysosomal proteolytic activity, which leads to the accumulation of autophagic substrates and ballooning of lysosomes. SWNT restores normal cellular autophagy and clears faulty proteins. Activating autophagy is an effective approach for removing pathological proteins and is more commonly used in the fight against AD. In addition to restoring normal autophagy, nanomaterials can also reduce levels of misfolded proteins by restoring lysosomal membrane integrity. Increased lysosomal membrane permeability leads to the release of lysosomal enzymes into the cytoplasm, triggering apoptosis (Gómez-Sintes et al., 2016; Sarkar et al., 2020). It has been shown that nanomaterials targeting lysosomes, such as PLGA, can protect lysosomal membranes and reduce the levels of misfolded proteins in cells (Wang et al., 2020; Wu et al., 2022). Furthermore, the accumulation of A β and tau proteins is a central pathophysiological feature of AD. Proteinopathies are characterized by the presence of misfolded and aggregated proteins, which lose their normal physiological functions and acquire neurotoxic properties. Researchers are focused on exploring novel mechanisms to facilitate the elimination of neurotoxic proteins, aiming to develop methods that can potentially mitigate the onset and slow the progression of AD.

In summary, lysosomal dysfunction and the accumulation of misfolded proteins are common pathological features of AD. Nanomaterials that target lysosomes can remove pathological proteins by reactivating lysosomes and enhancing cellular autophagy, which provides a more effective treatment for AD.

Inflammation modulation

Neuroinflammation is a physiological response that occurs inside the central nervous system in response to various pathogenic stressors. The contributory aspects include infection, trauma, ischemia, and toxins. The aforementioned process is distinguished by the generation of proinflammatory cytokines and chemokines. Furthermore, this procedure entails the secretion of small molecular signaling molecules, such as prostaglandins and nitric oxide, along with the infiltration of reactive oxygen species generated by innate immune cells into the central nervous system. The cellular constituents primarily implicated in this process encompass microglia and astrocytes, which are essential constituents of the innate immune system. Notably, capillary endothelial cells and infiltrating blood cells also contribute to neuroinflammation, particularly in instances when there is biochemical or mechanical impairment to the BBB (Heneka et al., 2014; DiSabato et al., 2016). The generation of proinflammatory molecules has the potential to impede synaptic dysfunction, induce neuronal demise, and impact neurogenesis (Lyman et al., 2014). The synaptic loss induced by interleukin (IL)-1 β is mediated by the increased expression of prostaglandin E2 production, resulting in heightened release of presynaptic glutamate and subsequent activation of postsynaptic N-methyl-d-aspartate receptors (Mishra et al., 2012). Added to that, the activation of the complement system can induce the enhancement of microglia's phagocytic function, potentially leading to inappropriate synaptic pruning (Hong et al., 2016).

Throughout the progression of neuroinflammation, a substantial quantity of anti-inflammatory cytokines, such as IL-1 receptor antagonists, IL-4, IL-10, and IL-11, are generated. The involvement of these cytokines in preventing excessive neuroinflammation highlights the existence of a complex regulatory system (Figure 7A; Calsolaro and Edison, 2016). Based on current research on neuroinflammation, it is evident that collaborative interactions among microglia, astrocytes, and neurons contribute to the progression of neurodegenerative processes.

According to *in vivo* data, nanoformulations have led to a reduction in inflammation. Vilella et al. (2018) developed a PLGA system modified with g7 glycopeptide for delivering zinc to the brain. By accessing the brain and increasing zinc levels, this system effectively reduced the presence of proinflammatory cytokines. In their study, Vilella et al. (2018) investigated the effects of zinc levels on inflammation in APP23 mice. They quantified the levels of IL-6, IL-18, tumor necrosis factor and IL-10 in wild-type mice, APP23 mice treated with g7-NPs or saline solution, and APP23 mice treated with zinc NPs. The researchers found evidence suggesting that g7-NPs-Zn can attenuate proinflammatory responses and enhance the production of anti-inflammatory cytokines, thereby exerting a counteractive effect on inflammatory mechanisms in the body (Figure 7B–E). Additionally, Wu et al. (2022) observed that the application of PLGA to neurons resulted in the downregulation of several transcripts associated with mediating neuroinflammation (e.g., interferon gamma, IL-1 alpha, and IL-6 compared to controls; Figure 7F).

The above studies show that nanomaterials can reduce neuroinflammation through different pathways and have a wide range of applications in the treatment of AD. They also show that nanomaterials can inhibit neuroinflammation through different mechanisms (e.g., diminishing cellular proinflammatory factors or increasing the levels of anti-inflammatory factors) and are highly prospective in the treatment of AD.

Nanomaterial-mediated lysosomal autophagy and neuroprotection

The prevalence of AD increases with age (Soria Lopez et al., 2019). This irreversible condition is characterized by the progressive degeneration and eventual death of neuronal cells. Neurodegenerative diseases are currently being treated with neuroprotective drugs, which may retard or prevent the progression of these diseases. Nanomaterials play a crucial role in providing neuroprotective drugs for neurodegenerative diseases due to their advantageous properties, such as their small size, biocompatibility, and low cytotoxicity (Xi et al., 2022; Anwar et al., 2023). Several studies have synthesized PLGA nanomaterials that encapsulated thymoquinone, a phytochemical molecule known for its antioxidant and anti-inflammatory effects, with the aim of targeting this specific aspect in animal models (Elbol et al., 2020; Yusuf et al., 2021). Their results demonstrated that thymoquinone could provide neuroprotection by reducing A β plaques, improving neuronal survival, and restoring neuronal activity. Additionally, Xue et al. (2014) utilized SWCNTs to treat AD model mice. These carbon nanotubes exhibited high water solubility and dispersibility, enhancing cellular autophagic flow. This property represents a potential mechanism through which neuroprotection can be achieved. Collectively, these nanomaterials demonstrated the ability to protect neurons in AD mice by mitigating neuronal loss and promoting neuronal viability. Although research on nanosizing neuroprotective compounds is still in its early stages, it holds significant potential for future advancements in pharmacology, particularly in the treatment of neurodegenerative diseases.

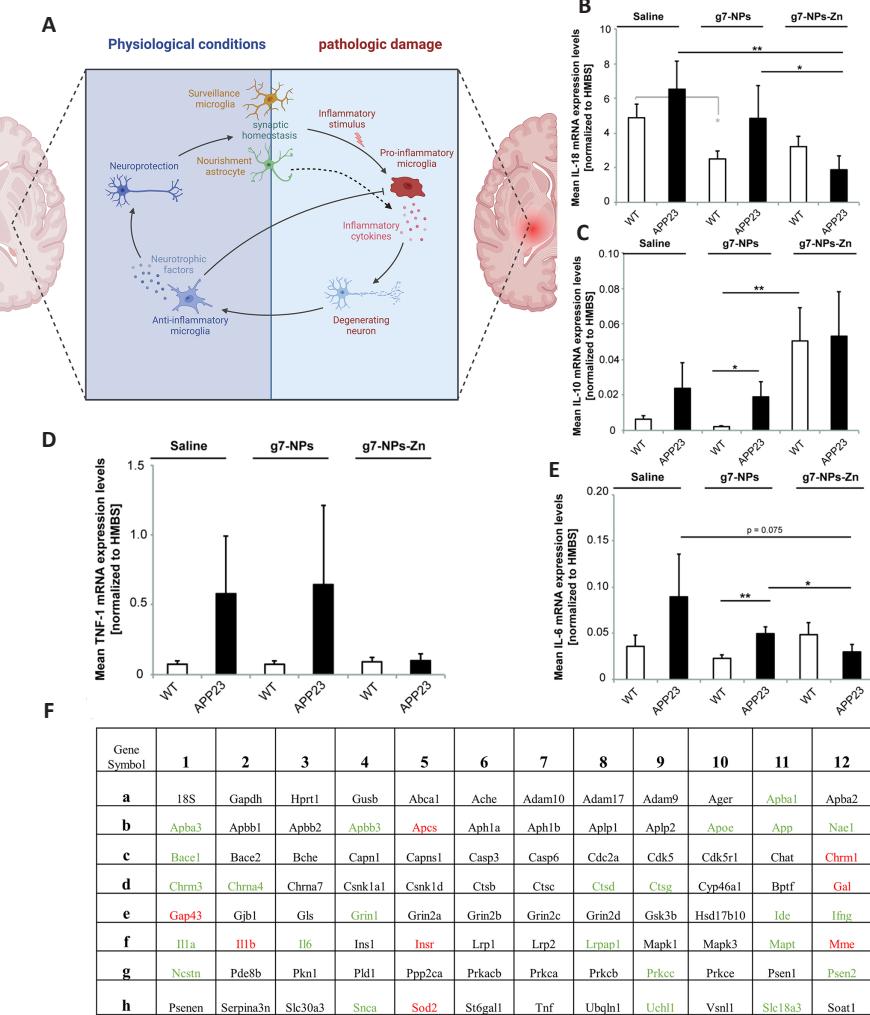


Figure 7 | Nanomaterials suppress neuroinflammation.

(A) Glial cells and their physiological functions. A was created with BioRender.com. (B–E) The treatment of animals with zinc-loaded nanomaterials altered inflammatory markers. * $P < 0.05$, ** $P < 0.01$. B–E were reproduced with permission from Vilella et al. (2018), Copyright 2017 Elsevier GmbH. All rights reserved. (F) Gene expression after 24 hours of PLGA treatment is shown in the following table. F was reproduced with permission from Wu et al. (2022), Copyright 2022 Published by Elsevier B.V. APP: Amyloid precursor protein; APP23: heterozygous APP23^{+/-} transgenic mice; g7: glycopeptide consisting of seven amino acids; HMBS: hydroxymethylbilane synthase; NP: nanoparticle; TNF-1: tumor necrosis factor 1; WT: wild type.

Conclusion and Outlook

As previously mentioned, the involvement of lysosomal dysfunction in the pathogenesis of neurodegenerative disorders has been implicated. Although the upregulation of autophagy has been observed as a compensatory response in these diseases (Bordi et al., 2016; Hou et al., 2020), it cannot be fully established when lysosomal function is impaired. Lysosomal dysfunction has emerged as a potential therapeutic target for various dementia-related conditions, including AD and PD (Lee et al., 2010; Nixon and Yang, 2012). Consequently, addressing lysosomal dysfunction has gained significant attention in the development of therapeutic interventions for neurodegenerative disorders.

Although nanomaterials enhancing lysosomal function have been effective in treating AD, their clinical application remains in its early stages, with most studies limited to *in vitro* and animal models. Several challenges need to be overcome to facilitate the clinical application of these nanomaterials. First, regarding polymeric nanomaterials, the most commonly used material is PLGA. PLGA is rapidly cleared by the reticuloendothelial system before reaching the brain (Ege, 2021). To prolong residence time and enhance brain transport, coadministration of PLGA with PEG is often employed. Although PEG can improve PLGA retention in the body, further research is necessary to thoroughly investigate the delivery efficacy, long-term toxicity, and pharmacokinetics of PLGA. Moreover, the byproducts generated during PLGA degradation may affect drug delivery to the brain (Mir et al., 2017), and their precise role needs to be elucidated. Second, the

utilization of carbon-based nanomaterials for AD therapy depends on addressing the existing challenges associated with these materials. Several experiments have demonstrated the potential toxicity of carbon nanotubes, inducing oxidative stress when co-cultured with cells. Ensuring high-quality carbon nanotubes and minimizing contaminants poses a significant challenge in their translational applications (Elsori et al., 2023). Therefore, researchers are focusing on improving the biocompatibility and safety of carbon nanotubes. Finally, NEs also face great challenges. They are less stable and susceptible to compromise by pH and temperature (Cunha et al., 2021b). Considering that lysosomes reside in acidic environments, these conditions may impact the stability and efficiency of NEs for drug delivery. Further experiments are essential to enhance the stability of NEs and improve the efficiency of drug delivery.

In conclusion, despite the immense potential of nanomaterials to target lysosomes in the treatment of AD, several challenges must be addressed before their clinical translation. These include optimizing the delivery efficacy and safety profile of polymeric nanomaterials, improving the biocompatibility and quality control of carbon-based nanomaterials, and enhancing the stability and efficiency of NEs for drug delivery. Overcoming these challenges, nanomaterial-based therapies targeting lysosomes could offer strategies for treating AD and other neurodegenerative disorders.

Lysosomal acidification and dysfunction are commonly observed in neurodegenerative diseases; growing evidence suggests that lysosomal dysfunction potentially contributes to

the development of these diseases. Consequently, targeting lysosomes has emerged as a strategic focus for potential therapeutic interventions in neurodegenerative disorders, such as AD. However, only a few studies have reported on drugs that specifically target lysosomal pH, and even fewer studies have examined nanomaterials targeting lysosomes. Despite the challenges faced by nanomaterials, they offer new possibilities and approaches for drug development in neurodegenerative and other brain diseases. Recent studies have shown that nanomaterial functionalization with peptides can effectively address issues such as low targeting efficiency and cytotoxicity. For example, in one study, D1 peptides were employed to functionalize magnetic nanomaterials, combined with chitosan-functionalized gold nanorods to effectively reduce cytotoxicity (Hassan et al., 2018). Moreover, the multimerization of compounds can enhance drug delivery, bioactivity, and tolerability at low concentrations by addressing the multivalency of biological targets. Therefore, nanomaterial functionalization

plays a crucial role in the development of AD drugs. In designing lysosome-targeted nanodrugs, researchers can refer to the aforementioned approaches to functionalize nanodrugs, thereby reducing drug toxicity and improving targeting efficiency. Our objective is to advance the development of nanomaterials that possess characteristics, such as low cytotoxicity, enhanced targeting capabilities, and improved stability. These nanomaterials are intended for the treatment of neurodegenerative disorders, particularly AD, by specifically targeting lysosomes. The utilization of nanomaterials designed to target lysosomes is anticipated to significantly impact AD therapy, thanks to advancements in materials science and synthesis methodologies.

Recently, nanomaterials have brought renewed hope in treating AD. This paper presents a detailed description of several types of nanomaterials targeting lysosomes (Figure 8), a crucial aspect of AD therapy. In addition, this paper also summarizes the development of targeted lysosomal drugs (Figure 9). These nanomaterials exhibit high cellular absorption, mobility, and

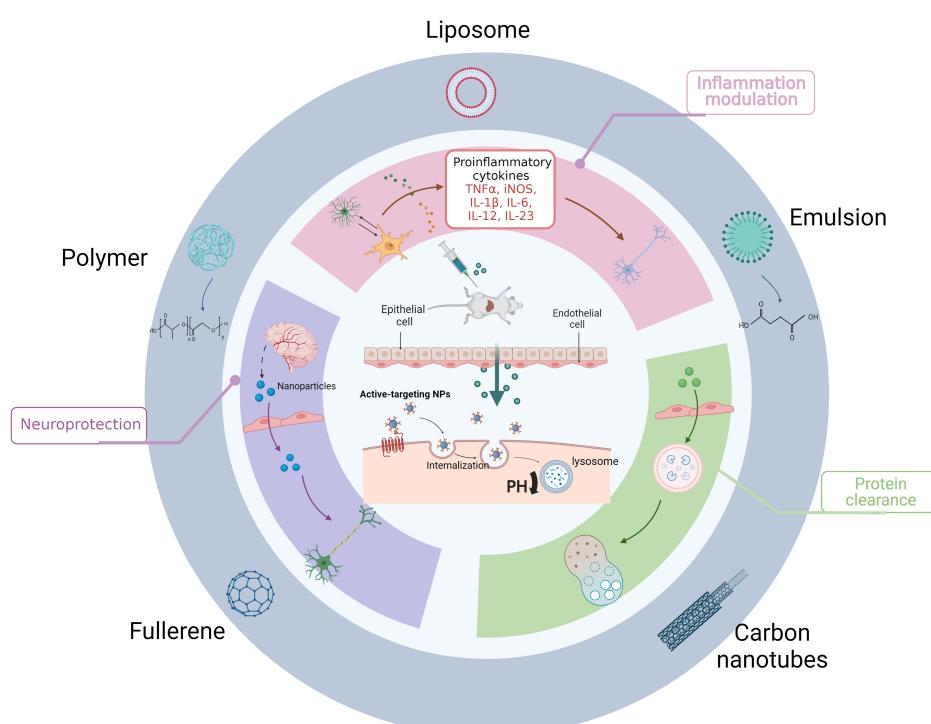


Figure 8 | Nanomaterials therapeutic pathway.

Nanomaterials are injected into mice, and after penetrating the blood-brain barrier, it reaches cells in the diseased areas of the mouse brain, reduces the pH of lysosomes, restores the cells' ability to clear proteins, reduces neuroinflammation, and protects nerve cells. Created with BioRender.com. IL: Interleukin; iNOS: inducible nitric oxide synthase; NP: nanoparticle; TNF- α : tumor necrosis factor- α .

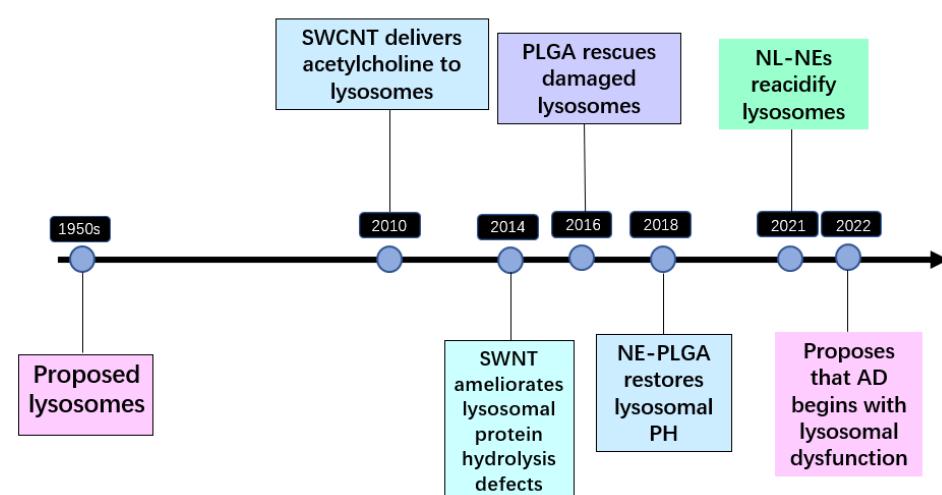


Figure 9 | Development of nanomaterials to restore lysosomal function in AD therapy.

Created with Microsoft PowerPoint. AD: Alzheimer's disease; NE: nanoemulsions; NL: nucleolipid; PLGA: poly(DL-lactide-co-glycolide); SWCNT: single-walled nanotube; SWNT: single-walled carbon nanotubes.

passive targeting, distinguishing them from small compounds that target the lysosome. Preliminary findings on the application of lysosome-targeted nanomaterials in various diseases, including lysosomal storage diseases, cancer, neurodegenerative diseases, and autoimmune diseases, highlight the therapeutic potential of these interventions. Existing pharmaceutical treatments for neurodegenerative diseases only provide temporary relief without offering a definitive cure. However, the utilization of nanomaterials specifically targeting lysosomes holds promise to improve this situation. This study anticipates to contribute to a comprehensive understanding of the field, stimulating novel ideas for the development of nanomaterials in biomedical applications related to lysosomes. Nevertheless, the intricacies of lysosomal function may be influenced by interactions among central nervous system cells, necessitating further research to explore these complex relationships. Additionally, drug targeting is crucial for delivery, and this review only briefly describes the targeted modification of nanomaterials, a topic not extensively explored and requiring further research.

Author contributions: Manuscript design: MH, JC, YL, JZ, JG, YY; data retrieval: TZ, TY, YG, WL, WJ, JZ, YL; manuscript preparation: MH, JC, TZ, YG; manuscript review: MH, JC, TZ, YL, YG, WJ, TY, WL, JZ, YY, JG; funding acquisition: YY, JG. All authors have read and approved the final version of the manuscript.

Conflicts of interest: All authors declare no conflicts of interest.

Data availability statement: Not applicable.

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