International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Mitochondria-Targeted Nanosystems in the Treatment of Central Nervous System Diseases

Xiaolan Zhang[1,*], Jiahui Chen[2,*], Bingjie Wan[1], Yanrong Zheng[1], Xiaojie Chen[1]

[1]Zhejiang Collaborative Innovation Center for the Brain Diseases with Integrative Medicine, Zhejiang Key Laboratory of Neuropsychopharmacology, School of Pharmaceutical Sciences, First Affiliated Hospital of Zhejiang Chinese Medical University, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, 310053, People's Republic of China; [2]College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, Zhejiang, 310058, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yanrong Zheng; Xiaojie Chen, Email yanrong_zh@zju.edu.cn; chenxiaojie0902@163.com

Abstract: Mitochondrial dysfunction represents a pivotal pathological mechanism underlying diverse diseases, particularly those affecting the central nervous system (CNS). Consequently, therapeutic strategies capable of effectively restoring mitochondrial function hold significant promise for treating CNS disorders. Nanotechnology has emerged as a powerful platform in this endeavor, leveraging the modifiability, controllability, and targeting capabilities of nanosystems to intervene at the mitochondrial level. This review delineates the critical role of mitochondrial integrity in CNS pathophysiology and summarizes key mitochondria-targeting strategies, including small-molecule ligands, mitochondrial-penetrating peptides, mitochondrial membrane-derived vesicles, and biomimetic membrane coatings. We also discuss the efficacy of mitochondria-targeted nanosystems in rescuing mitochondrial dysfunction across major CNS conditions, exemplified by neurodegenerative diseases, brain tumors, ischemic stroke, and traumatic brain injury. Ultimately, this review also points out current translational challenges and future research directions pivotal for advancing mitochondrial nanomedicine. Collectively, this work synthesizes progress in mitochondrial nanotherapeutics, highlighting their transformative potential while outlining critical barriers and opportunities for clinical translation in CNS disorders.

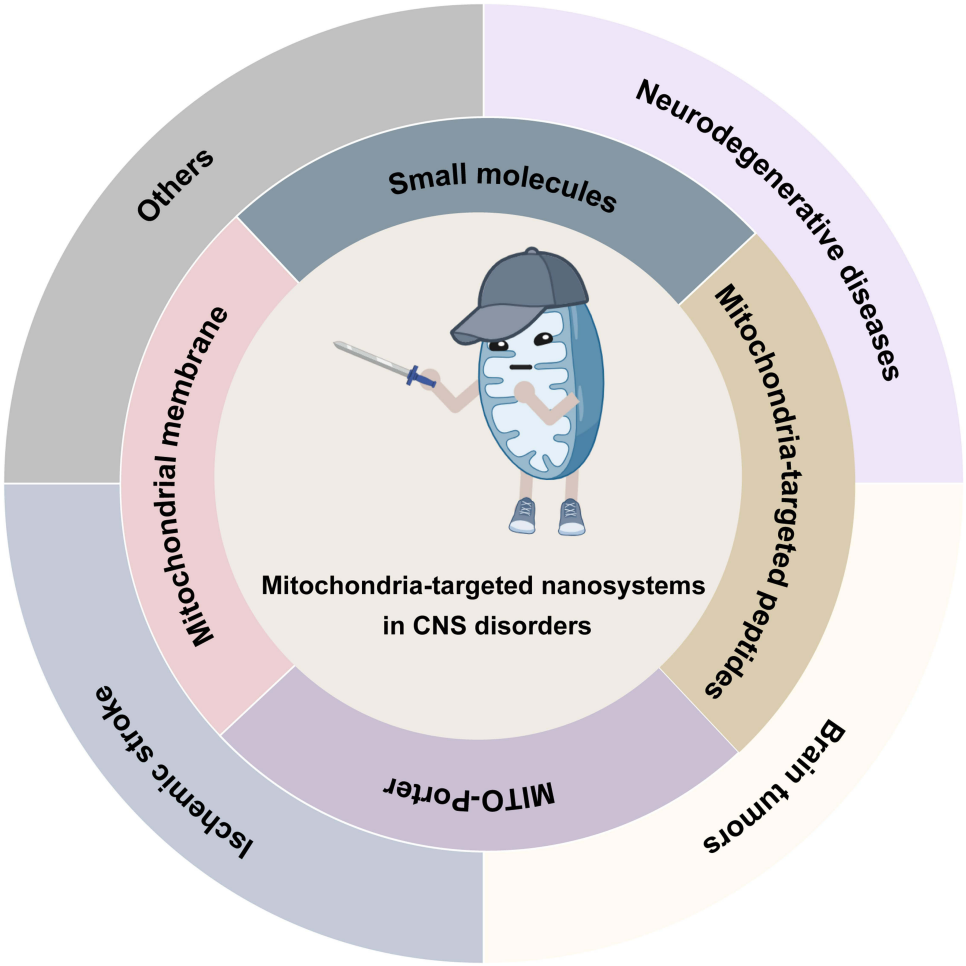
Keywords: Mitochondrial dysfunction, Mitochondria-targeted therapy, Nanosystems, Drug delivery

Introduction

When mitochondria are mentioned, their name comes to mind naturally as "powerhouse". As is well known, they are semi-autonomous organelles enclosed by two membranes, possessing own genetic material and found in most eukaryotic cells. Mitochondria provide adenosine triphosphate (ATP) to cells and serve as the primary site for aerobic respiration, with a diameter of approximately 0.5 to 1 micrometer.[1,2] ATP production occurs through oxidative phosphorylation (OXPHOS) and the tricarboxylic acid (TCA) cycle. In the inner mitochondrial membrane, the electron transport chain (ETC) transfers electrons from reduced coenzymes (NADH and $FADH_2$) to oxygen, driving proton pumps to form a transmembrane proton gradient, which ultimately synthesizes ATP through ATP synthase.[3,4] Mitochondria are not only the centers of energy metabolism but also participate in various cellular processes such as calcium ion homeostasis, apoptosis, and reactive oxygen species (ROS) regulation.[5,6] They play a dual role in maintaining physiological homeostasis and mediating pathological damage, thereby determining the survival and death of cells. Mitochondrial dysfunction, characterized by oxidative stress, abnormal energy metabolism, and impaired apoptosis, is a key pathological mechanism in neurodegenerative diseases, cancer, and cardiovascular and kidney disorders. Under pathological conditions, ETC dysfunction leads to energy crises and ROS surges, while mitochondrial dynamics imbalance (abnormal fusion/fission) and autophagy defects contribute to neurodegeneration. Studies have shown that the frequency and duration of the mitochondrial permeability transition pore (mPTP) opening are correlated with increased ROS production, electron leakage, and a reduction in mitochondrial membrane potential (MMP), collectively precipitating cellular

Received: 26 August 2025
Accepted: 25 November 2025
Published: 8 December 2025

Graphical Abstract



apoptosis.[7] Zhou et al discovered that the transcription factor Nynrin is highly expressed in hematopoietic stem cells, with further upregulation under stress conditions such as radiation. Nynrin serves as a key regulator in maintaining HSCs by modulating mitochondrial function. Deficiency of Nynrin leads to a reduction in HSC numbers, loss of quiescence, impaired self-renewal capacity, and mitochondrial dysfunction characterized by increased mPTP opening, mitochondrial swelling, and elevated ROS levels.[8] Strategies targeting MMP restoration, mtDNA protection, regulate the opening of mPTP, and quality control pathway activation offer novel therapeutic avenues.[9]

Central nervous system (CNS) diseases, including neurodegenerative diseases, brain tumors, and cerebrovascular lesions, pose significant global public health challenges due to their high disability and mortality rates.[10–12] The common pathological features of these diseases are closely related to mitochondrial dysfunction. For instance, mitochondria in the brain of patients with Alzheimer's disease (AD) differ significantly in number and morphology from those in healthy individuals.[13] Amyloid-β (Aβ) oligomers in the brains of AD patients induce abnormal opening of the mPTP, leading to calcium overload and neuronal apoptosis.[14,15] In Parkinson's disease (PD), abnormal α-synuclein aggregation disrupts mitophagy, leading to accumulated damaged mitochondria in dopaminergic neurons.[16,17] Post-stroke ischemia-reperfusion generates excessive ROS that directly damages mtDNA, exacerbating neuronal death.[18,19] These findings collectively underscore mitochondria as central targets for treating CNS diseases.

Nano-drug delivery systems have emerged as key tools for CNS therapy, enhancing drug bioavailability and retention while enabling site-specific delivery via modifications with peptides, membranes, or microenvironment-responsive

ligands.[20,21] Notably, due to the presence of blood-brain barrier (BBB), over 98% of small-molecule drugs and nearly all large-molecule therapeutics struggle to effectively reach brain lesions. Therefore, precise mitochondrial interventions in CNS diseases face dual challenges, including overcoming the BBB's biological bottleneck, and further achieving subcellular-level precision delivery.[22] Most previous studies have reviewed the strategies for nanomaterials crossing the BBB, which could be achieved via carrier, receptor or cell-mediated transcytosis, as well as some external modulation strategies.[23–25] Mitochondria-targeted nanosystems are emerging as promising therapeutic approaches for mitochondria-related disorders treatment.[26–28] These nanosystems have the potential to directly deliver drugs to mitochondria, reduce oxidative stress of mitochondria, and restore energy homeostasis.[29]

This review discusses the design principles and applications of mitochondria-targeted nanosystems, with a focus on their use in CNS diseases (Figure 1). We aim to provide insights for researchers in mitochondrial-targeted therapy and inspire future designs of precision delivery platforms.

Design Principles and Applications of Mitochondria-Targeted Nanosystems

Mitochondria have a double-membrane structure consisting of the outer mitochondrial membrane (OMM) and inner mitochondrial membrane (IMM). Both membranes are primarily composed of proteins and lipids. The space between them is termed the inter-membrane space (IMS), while the IMM is subdivided into the inner boundary membrane (IBM), cristae junctions (CJs), and cristae.[30] Porins (eg, VDAC) are abundant on the OMM, allowing free diffusion of substances <5 kDa. In contrast, the IMM exhibits extremely low permeability and high tortuosity with only specific molecules (such as O_2, CO_2) passively diffusing while other substances rely on transport proteins. Located in the IMM, the mPTP is a non-selective channel formed by large protein complexes. It critically regulates apoptosis—aberrant opening mediates leakage of pro-apoptotic factors (eg, Cytochrome C/Cyt C) from the IMS into the cytoplasm, activating apoptotic cascades. The IMM also houses oxidative phosphorylation machinery and is enriched with cardiolipin, a phospholipid essential for OXPHOS complex stability.[31]

Mitochondria-targeted nanosystems usually employ four key strategies, namely (1) small-molecule ligands (eg, triphenylphosphonium/TPP), which exploit the IMM's negative membrane potential to accumulate drugs in the matrix; (2) peptide ligands that leverage lipophilicity/cationic properties; (3) mitochondrial membrane-derived vesicles; and (4) biomimetic membrane systems. The latter two utilize natural membrane components (eg, proteins, lipids) for intrinsic homing to mitochondria. Herein, we discuss the design principles of these nanosystems and summarize their applications (Table 1).

Small Molecules

TPP

Owing to the transmembrane potential ($\Delta\psi m$) of −150 to −180 mV (matrix negative relative to cytoplasm) across the IMM, lipophilic cations accumulate in the mitochondrial matrix via electrophoresis. Their delocalized surface charge enables lipid bilayer penetration, driving selective enrichment via the electrochemical gradient.[32,60]

Meanwhile, the unique electrochemical properties of mitochondria provide feasibility for the targeted delivery of antioxidant molecules. This is achieved by chemically coupling therapeutic molecules with lipophilic cations, which enables selective accumulation through the membrane potential of mitochondria, thereby establishing a specific protective mechanism against mitochondrial oxidative damage.[32,61] TPP, as a targeting moiety, delivers various antioxidants into mitochondria and accumulates within mitochondrial organelles. As one of the most common mitochondria-targeted molecules, TPP is an organophosphate compound with a lipophilic cation that can effectively target mitochondria through electrostatic interactions. The key mechanism behind its targeting strategy stems from the electrochemical characteristics of the IMM.[62] So far, research on using TPP as a mitochondria-targeted modification has been extensive. TPP can be modified on various nanocarriers such as liposomes, inorganic nanoparticles, micelles, and other polymer nanoparticles. A common strategy for modifying liposomes with TPP involves synthesizing TPP-PEG-PE or TPP-PEG-DSPE first to improve the stability and targeting efficiency of the carrier by coupling it with other groups. When inorganic nanoparticles are used as carriers, the modification methods usually include direct coupling and indirect modification techniques. Inorganic nanoparticles featuring -COOH, $-NH_2$, or -SH groups on their surface are suitable

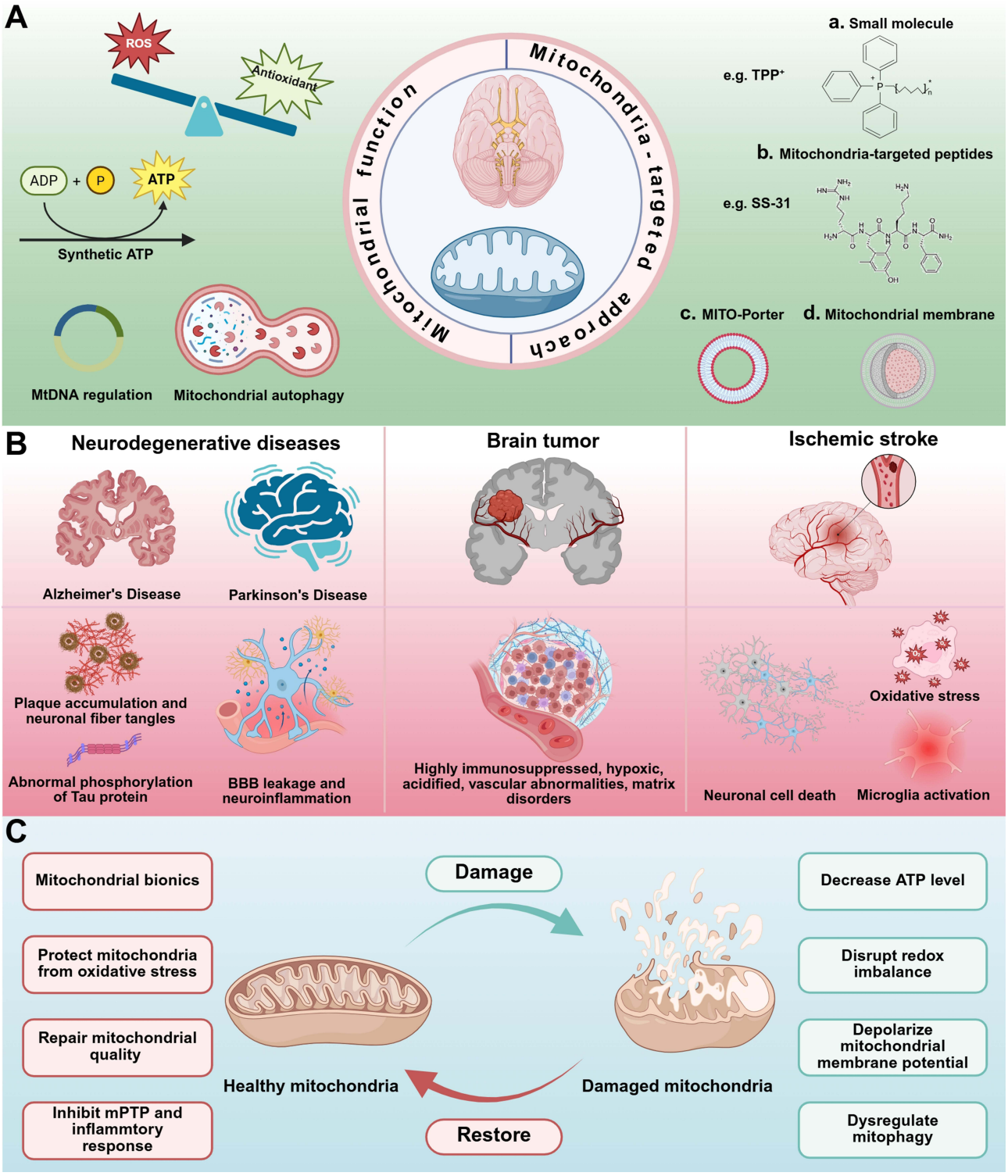


Figure 1 Schematic illustration of mitochondria-targeted nanosystems in CNS disorders. (**A**) Mitochondrial function and mitochondria-targeted approaches. (**B**) The microenvironment of mitochondria-related CNS diseases. (**C**) The role of mitochondria-targeted nanosystems in regulating the mitochondria function. Created with BioRender.com.

for direct coupling. For example, Xia et al[33] utilized TPP coupled with DSPE-TK-PEG2000 to achieve mitochondrial targeting and demonstrated ROS-responsive effects via the thioketal (TK) bond. They developed a drug delivery system using nanoliposomes to deliver tripterygium glycoside to mitochondria for treating hepatocellular carcinoma. It was

Table 1 Representative Mitochondria-Targeted Groups

Type	Targeting Group	Mechanism	Modification Methods	Reference
Small molecule	TPP	Lipophilic cation, membrane potential driven	Liposomes / micelles: TPP-PEG-PE, TPP-PEG-DSPE Inorganic nanoparticles: covalent conjugation, eg, TPP-COOH	[32–35]
	Rhodamine 123	Lipophilic cation, membrane potential driven	Liposomes / micelles: Rh123-PEG-DOPE Inorganic nanoparticles: covalent conjugation	[36–39]
	TMRM	Lipophilic cation, membrane potential driven	Liposomes / polymer nanoparticles: Physical co-loading, covalent conjugation	[40]
	F16	Lipophilic cation, membrane potential driven	Mainly conjugated to drug molecules through chemical synthesis	[41,42]
	DQA	Bicationic amphiphilic molecule	Liposomes / micelles: Covalent conjugation to lipid materials (eg, DSPE-PEG) polymer nanoparticles: chemical conjugation	[43,44]
	MitoQ	TPP and ubiquinone conjugates	Similar to TPP	[45]
	Mito-Vit-E	TPP and vitamin-E analog conjugates	Similar to TPP	[46]
	SkQ1	TPP and plastoquinone conjugates	Similar to TPP	[47]
	Mito-TEMPOL	TEMPOL nitroxides tethered to TPP+	Similar to TPP	[47]
Peptides	SS-31	Cationic and lipophilic	Covalent connection and hydrophobic insertion	[48–51]
	MPPs	Cationic and lipophilic	Physical Encapsulation, electrostatic adsorption, covalent conjugation	[52,53]
	XJB-5-131	Mimics the membrane lipid affinity of the antibiotic gramicidin S	Can be used independently	[54–56]
Vesicles and membrane mimetic systems	Mito-Porter	Mitochondria-targeted ligand modification	Covalent conjugation, electrostatic adsorption	[57]
	Mitochondrial membranes	Homologous targeting	Physical Encapsulation	[58,59]

shown that modifying the liposome surface with TPP-PEG2000-TK-DSPE could significantly enhance the aggregation ability of these liposomes in mitochondria. Li et al synthesized TPP-modified micelles loaded with puerarin for the treatment of acute myocardial infarction, they likewise began by synthesizing the mitochondriotropic polymer TPP-PEG-PE. Compared to free puerarin, these micelles exhibited enhanced cellular uptake, improved mitochondrial targeting, and increased lysosomal escape.[34] However, this method requires multi-step organic synthesis, more complex preparation processes and higher costs. In Gu et al's study[35] bimetallic cluster nanozymes were employed to reduce neuropathic pain. TPP was pre-modified to TPP-COOH and then covalently linked to the surface of bimetallic cluster nanozymes. Covalent bonds give it high stability and prevent TPP from detaching in the internal environment. Nevertheless, it is important to note that TPP is inherently a cationic species. High-density TPP modification also carries potential toxicity, as it may disrupt mitochondrial membrane integrity, thereby impairing the respiratory chain and ATP synthesis. This cascade of events can ultimately lead to cellular dysfunction or apoptosis. Furthermore, TPP may exhibit metabolic instability in vivo and has a limited ability to cross the blood-brain barrier, posing a significant challenge for treating brain disorders.[63,64]

Besides TPP, other antioxidants, including ubiquinol, alpha-tocopherol, vitamin C, metformin, and tempol, have also been investigated.[32,65,66] The combination of lipophilic cations and antioxidants is applied in the treatment of various diseases, such as chronic obstructive pulmonary disease, traumatic brain injury, inflammatory bowel disease, cardiovascular diseases, renal ischemia-reperfusion injury, PD, AD.[67–73]

Other Cationic Targeting Molecules

Rhodamine, initially discovered as a dye in 1887, was later utilized as a probe.[74] Rhodamine 123 belongs to the rhodamine dye family and is a lipophilic cationic compound that accumulates in mitochondria in a mitochondrial membrane potential-dependent manner, serving as a fluorescent probe for monitoring membrane potential in living cells. Later, it was also gradually used for mitochondria-targeted modifications. Similar to TPP, it can be linked to drugs through chemical coupling or modified liposomes, polymer nanoparticles, and other carriers in a similar fashion.[36,37,75,76]

https://doi.org/10.2147/IJN.S562666

Another derivative of rhodamine, tetramethyl rhodamine methyl ester (TMRM), functions similarly to Rhodamine 123. Its structure includes a tetramethyl-substituted rhodamine skeleton with methyl ester groups. As a cationic dye, TMRM enriches in the mitochondrial matrix with a higher negative potential through electrochemical gradients, and its fluorescence signal can quantitatively reflect changes in MMP.[40,77–79] TMRM can be conjugated to other molecules, such as polymers and drugs, through functional group reactions to form functional probes or drug delivery systems. Additionally, F16 and its analogs are used for mitochondrial tracing and serve as mitochondria-targeted anticancer agents, primarily effective against cancer.[80–82] F16 is mainly conjugated to drug molecules through chemical synthesis, thereby enhancing its mitochondrial targeting and antitumor activity.[41,83]

Moreover, dequalinium (DQA) is another cationic mitochondria-targeted molecule—a bis-quaternary ammonium compound with two positively charged quaternary ammonium groups and a hydrophobic carbon chain, combining hydrophilicity with hydrophobicity. DQA can be used in nanoemulsions or liposome assemblies.[84–86] A distinctive application of DQA is its ability to self-assemble in aqueous solution to form vesicular structures known as DQAsomes, which are used for the delivery of genes or small-molecule drugs.[87] DQA can be covalently linked directly with lipids, such as DSPE-PEG, modified on the surface of liposomes, and form mitochondria-targeted carriers. In polymer nanoparticles, such as polylactic acid-glycolic acid copolymer, DQA binds to the carriers through electrostatic interactions or chemical coupling.[43,88] Although these small molecules exhibit good mitochondria-targeting abilities, their potential toxicity due to their cationic properties limits their further applications.[89]

Mitochondria-Targeted Peptides

SS Peptides (with SS-31 as a Representative)

Mitochondria-targeted peptides (MTPs) are short peptides engineered to deliver therapeutics or modulate mitochondrial functions. Their design leverages mitochondrial membrane properties or natural targeting signals. Szeto-Schiller (SS) peptides, exemplified by tetrapeptides with alternating aromatic (eg, phenylalanine and tyrosine) and basic (eg, lysine and arginine) residues, exhibit potent molecular recognition and membrane penetration.[90] They specifically target the IMM via lipophilic-cationic structures and confer mitochondrial protection through dual mechanisms.[91] On the one hand, they can directly eliminate mitochondrial ROS and inhibit their excessive generation. On the other hand, SS peptides can maintain mitochondrial membrane integrity by blocking pathological mPTP opening. Critically, SS peptides mitigate apoptosis and necrosis triggered by oxidative stress or ETC dysfunction,demonstrating efficacy in ischemia-reperfusion, neurodegeneration (AD/PD), cognitive deficits, and renal fibrosis models with high biocompatibility.[91,92] Szeto-Schiller Peptide 31 (SS-31, also known as MTP-131, elamipretide), a representative aromatic cationic peptide, selectively binds cardiolipin on the IMM via electrostatic interactions driven by its alternating cationic/aromatic structure.[58,93–96] This targeting mechanism operates independently of strict membrane potential dependence. SS-31 is frequently conjugated to nanocarriers (eg, liposomes, micelles, or polymer nanoparticles) to enhance mitochondrial targeting efficiency through the synergistic effect of passive targeting of nanocarriers (eg, enhanced permeability and retention effect) and active targeting of SS-31.[97–99] Methods for conjugating it to nanocarriers primarily include covalent connection and hydrophobic insertion. For example, in polymer nanoparticles, SS-31 can be connected to the particle surface through chemical coupling of amino or carboxyl groups (such as EDC/NHS reaction). It is also possible to covalently link the cysteine residues on SS-31 with DSPE-PEG_{2000}-Mal (maleimide group) in the liposome formulation through thioether bonds.[48,49,100,101] SS-31 has a favorable safety profile and is considered a promising strategy for the treatment of diabetic cardiomyopathy. Xiong et al revealed a novel mechanism of mitochondria-targeted peptide SS-31 for the treatment of diabetic cardiomyopathy (DCM): SS-31 inhibits mitochondrial lipid peroxidation and attenuates mitochondria-dependent ferroptosis through specific activation of mitochondrial glutathione peroxidase 4 (mitoGPX4). In a diabetic cardiomyopathy model, high glucose and metabolic disorders lead to enhanced mitochondrial oxidative stress, imbalanced iron metabolism, and reduced mitoGPX4 activity, which in turn triggers ferroptosis in cardiomyocytes. SS-31 restored the antioxidant function of mitoGPX4 by targeting mitochondria and stabilizing the structure of cardiolipin, reduced mitochondrial ROS and lipid peroxidation accumulation, as well as inhibited the expression of key markers of ferroptosis, thereby protecting cardiomyocytes from ferroptosis-driven injury. The experimental results showed that SS-31 significantly improved cardiac function, attenuated myocardial fibrosis and mitochondrial structural disruption in diabetic mice, and provided a novel strategy for targeting mitochondrial

ferroptosis in the treatment of DCM.[102] In addition, Zhu et al summarized that, as a mitochondria-targeted antioxidant, SS-31 alleviates oxidative stress by inhibiting the overproduction of mitochondrial ROS, repairing the function of the mitochondrial electron transport chain to enhance ATP synthesis, inhibiting mitochondrial membrane permeability transition pore opening and down-regulating inflammatory factors expression, thereby reducing oxidative stress damage to renal tubular epithelial cells and podocytes, as well as attenuating renal inflammatory responses, suggesting that SS-31 may be a candidate for the treatment of mitochondria-associated nephropathy, providing a new direction in the treatment of nephropathy.[103] Currently, SS-31 has been widely used in the treatment of mitochondrial dysfunction-related diseases in various systems, such as the nervous and cardiovascular systems. Du et al systematically explored the mechanism of action and efficacy of the novel mitochondria-targeted antioxidant peptide SS-31 in alleviating mitochondrial dysfunction, highlighting the broad prospects of SS-31 as a therapeutic tool for precisely regulating mitochondrial function in the treatment of mitochondrial-related diseases.[104] Furthermore, many nano-delivery systems utilize the mitochondria-targeting ability of SS-31 to deliver drugs, genes or probes to the mitochondria in a targeted manner, which synergistically enhances the repairing effect on mitochondrial dysfunction with the delivered agents, reduces systemic toxicity and improves the bioavailability.[49,50,105–107]

XJB-5-131

XJB-5-131 is also a synthetic peptide and a mitochondrial-targeted antioxidant. Its structural design combines mitochondrial targeting and free radical scavenging functions. The molecular structure of XJB-5-131 is composed of two functional modules linked by chemical bonds. The mitochondrial-targeting moiety is a cationic oligopeptide structurally inspired by gramicidin S. It targets the negatively charged regions of the mitochondrial inner membrane via positively charged amino acid residues and binds to phosphatidylserine in the mitochondrial inner membrane through electrostatic interactions. The antioxidant active part is composed of nitroxide radicals. Usually, the targeted peptide is coupled with the antioxidant group through ester bonds or amide bonds to ensure the structural stability and functional synergy.[54,55,108,109] It targets mitochondria more rapidly and does not require a carrier, showing low toxicity and little interference with MMP. Besides, it is mainly utilized in relation to oxidative stress diseases, with its application in drug delivery being less explored and requiring further development.[110] It has been shown, XJB-5-131 is a novel mild oxidative phosphorylation uncoupler that partially disrupts the proton gradient in the IMM, thereby reducing ATP synthesis efficiency and increasing heat production, thus regulating mitochondrial energy metabolism.[54] Unlike potent uncoupling agents, XJB-5-131 exhibits controllable uncoupling effects at low doses, reducing ROS accumulation and alleviating oxidative stress damage while avoiding side effects such as excessive heat production and energy depletion. Experiments have shown that this compound selectively acts on mitochondrial membrane structures to improve cellular energy metabolism disorders and has demonstrated protective potential in models of neurodegenerative diseases and ischemic reperfusion injury. Its “mildness” makes it safer for treating metabolic syndrome and age-related diseases, but further research is needed on its long-term effects, tissue specificity, and clinical translation potential. Sun et al found that the mitochondria-targeting compound XJB-5-131 restored Pebp1 protein expression in chondrocytes, inhibiting ferroptosis (reducing lipid peroxidation products and upregulating GPX4 activity), thus protecting chondrocytes and alleviating osteoarthritis (OA) progression; in vivo experiments showed that XJB-5-131 joint injection significantly reduced cartilage degeneration and inflammation in mouse OA models with a favorable safety profile, providing a new strategy for OA treatment targeting ferroptosis.[111]

Mitochondrial-Penetrating Peptides, MPPs

Mitochondrial-penetrating peptides (MPPs) have been extensively studied as a means of mitochondrial uptake. MPPs are synthetic mitochondria-targeted peptides whose typical structure consists of 4–16 amino acid residues, which typically contain positively charged basic and hydrophobic amino acids. Studies have shown that the mitochondrial targeting efficiency of MPPs is closely related to their surface positive charge properties and hydrophobicity. MPPs, as a type of short peptides with the ability to penetrate both cellular and mitochondrial membranes, present diversified strategies in their mechanism of action and structural design. Innovative strategies based on the structural similarity between mitochondria and bacterial membranes have attracted attention, such as semi-Grammycin analogues designed to simulate Grammycin S. MPPs relies on the characteristics of positively charged amino acids and achieves delivery through

interaction with negatively charged mitochondrial membranes, which can enhance the precise accumulation of drugs in mitochondria and reduce off-target effects.[27,32,112] Zhou et al successfully developed a polymer-MPP-doxorubicin (P-M-Dox) coupling that achieved specific mitochondrial delivery through mitochondria-targeting properties and significantly improved doxorubicin delivery efficiency by circumventing the P-gp efflux pump effect.[113]

Advantages and Challenges of MTPs

Peptides targeting mitochondria have advantages such as high targeting efficiency, biocompatibility and stability, and avoiding the risk of genomic integration.[114–116] However, several concerns should be addressed issues. The mitochondrial targeting of some peptides mainly depends on the electrochemical potential of the electron transport chain, which may fail under pathological conditions (such as reduced membrane potential). Additionally, peptides tend to dissociate after binding to mitochondria, affecting sustained action. Off-target effects may also occur, as peptides may non-specifically bind to other negatively charged cellular structures or interfere with normal mitochondrial function. Furthermore, large-scale production is challenging.[112,115,117] There is still room for improvement in terms of structure, joint delivery systems, and dynamic response design.[96,118,119]

Mitochondria-Targeted Vesicles and Mitochondrial Membrane Mimetic Systems

MITO-Porter is a liposome-based mitochondrial targeting delivery system that encapsulates drugs in double-layer liposomes and is surface-modified with mitochondrial targeting ligands (such as mitochondrial signaling peptides or membrane fusion-related lipids), to achieve mitochondrial delivery.[57] The MITO-Porter system has been widely utilized in the field of mitochondrial targeting.[120] The core principle behind MITO-Porter's mitochondrial targeting lies in achieving specific delivery through the membrane fusion mechanism of lipid nanoparticles. It adopts a bilayer liposome structure, where surface-modified ligands (eg, octaarginine/R8) mediate binding to the outer mitochondrial membrane (OMM), followed by liposome-OMM fusion, which directly releases the cargo into the intermembrane space.[121–123] This mechanism overcomes the physical barrier posed by the mitochondrial bilayer membrane structure and avoids lysosomal degradation via the endocytosis pathway.[26] Yuma Yamada et al demonstrated mitochondrial gene therapy using MITO-Porter-encapsulated tRNA nanoparticles composed of DOPE, sphingomyelin, and stearylated R8 at a molar ratio of 9:2:1.[124] However, its poor stability, limited drug loading capacity, and difficulty in delivering hydrophilic drugs restrict further applications.[58]

Biomimetic cell membrane encapsulation technology, which leverages the integration of natural membrane components and targeting mechanisms, has emerged as a promising approach to address these limitations.[125–127] Specifically, biomimetic cell membranes can confer immune evasion, prolonged circulation, and precise targeting capabilities on nanoparticles, thereby significantly enhancing delivery efficiency and reducing off-target effects.[128] This biomimetic design not only retains the characteristics of natural membranes but also overcomes the spatial resolution limitations of traditional delivery systems through biocompatible transport pathways.[129–132] Compared to whole cell membranes, mitochondria-derived membrane-coated nanosystems can deliver therapeutic molecules to mitochondria more efficiently, enabling precise subcellular-level drug delivery through membrane fusion-mediated intracellular transport mechanisms.[58] The extraction of mitochondrial membranes from cells typically involves two steps: first, cells are homogenized using a glass homogenizer; then, mitochondria are isolated via gradient centrifugation. Finally, mitochondrial membranes are obtained by ultracentrifugation at low temperature.[59,133] By leveraging the natural properties of mitochondrial membranes to achieve homologous targeting, existing research has explored methods for directly wrapping nanoparticles with membranes to enhance targeting, including co-extrusion and sonication.[134–137] Chen et al reported a mitochondrial-mimicking therapeutic strategy capable of specifically targeting dilated cardiomyopathy and effectively regulating mitochondrial homeostasis.[138] They synthesized nano-micelles (TPTN) and achieved mitochondrial targeting in cardiomyocytes by encapsulating the micelles with OMM-derived vesicles. The surface of MTPTN is functionalized with OMM-specific proteins, which enable direct homophilic binding to their counterparts on the mitochondrial membrane of cardiomyocytes. This membrane-membrane recognition mechanism significantly enhances targeting specificity. In addition, by combining two types of membranes through methods such as sonication, extrusion, or a combination of both, multifunctional hybrid membranes can be constructed that integrate the inherent properties of both components.[139,140]

Shi et al developed hybrid membranes using cancer cell membranes and mitochondrial membranes to achieve dual targeting.[59] Mitochondrial membrane proteins integrated into the hybrid membranes—such as the outer membrane protein TOM20 and mitochondrial fusion-related proteins—mimic the natural surface features of mitochondria, promoting either membrane fusion or endogenous uptake between nanoparticles and mitochondria, thereby enabling subcellular organelle-level targeting. The inner and outer mitochondrial membranes contain various proteins and lipids that can be used for homologous targeting and lipid fusion. Targeted delivery using membrane-coated nanocarriers or membrane-fused liposomes can facilitate homologous targeting via antibody-antigen interactions.

Moreover, in addition to effectively deliver the therapeutics to mitochondria, some vesicles also have the property to rescue the mitochondrial dysfunction. Deng et al have proposed that the extracellular vesicles collected from mesenchymal stem cells (MSCs) with 3D dynamic culture could improve the proliferation ability and cell viability of aging-gingival MSCs, as well as ameliorate senescence. This effects was attributed to the up-regulated genes which were related to the mitochondrial dynamics, cell cycle and DNA repair functions.[141]

Mitochondria-Targeted Nanosystems for CNS Disorders

Given the central role of mitochondria in cellular energy homeostasis, mitochondria-targeted nanosystems show therapeutic potential for mitochondrial-related pathologies such as cancer, cardiovascular diseases, and brain disorders.[142,143] The substantial accumulation of nanoparticles in a subset of mitochondria disrupts mitochondrial network connectivity by inducing fragmentation, impairs calcium buffering capacity through persistent mPTP opening, and activates retrograde signaling to the nucleus via released ROS and Mitochondrial DNA (mtDNA). This mechanism can be therapeutically harnessed to either trigger apoptosis in cancer cells or protect neurons in neurodegenerative diseases by modulating mitochondrial function.[144,145] These nanosystems exert therapeutic effects by modulating energy metabolism, targeting mitochondrial DNA, regulating ROS, directing mitochondrial proteins, exerting anti-inflammatory effect, or enhancing mitophagy.[146,147] Compared with other organs, the brain is more sensitive and reliant on energy produced by mitochondria. Additionally, nearly 15% of global deaths are closely related to mitochondrial damage in brain diseases.[148] This section discusses applications of mitochondrial-targeted nanosystems in CNS disorders, including neurodegenerative diseases, brain tumors, and ischemic stroke (Table 2).

Before achieving the mitochondria of CNS-related cells, these nanosystems should bypass the first barrier of BBB. Recently, a variety of transport therapeutics have been developed for enhancing the BBB crossing ability of nanosystems, including adsorptive-mediated transcytosis, carrier-mediated transcytosis, receptor-mediated transcytosis, cell-mediated transcytosis, and modulation of tight junction.[180,181] However, the specific diseased BBB-based brain-targeting strategies should be designed based on the BBB evolutions of CNS diseases, which owing to that the diseased BBB of various CNS disorders is different and complex.

Neurodegenerative Diseases

Neurodegenerative diseases, including AD, PD, Huntington's disease (HD), and Amyotrophic Lateral Sclerosis (ALS), are a group of heterogeneous disorders caused by the progressive degeneration of neurons.[182] Mitochondrial dysfunction is closely associated with the progression of neurodegenerative diseases, leading to oxidative stress and impaired neuronal metabolic activity.[183] Consequently, mitochondria represent a promising target for therapies aimed at mitigating neurodegeneration. In recent years, various mitochondria-targeted nanosystems have been developed to modulate mitochondrial functions in neurodegenerative diseases, such as regulating calcium ion transport, delivering antioxidants, chelating metals, and modifying proteins.[184]

AD

As the most common neurodegenerative disease, AD is characterized by pathological aggregation of Aβ plaques and hyperphosphorylated Tau neurofibrillary tangles, as well as abnormally elevated ROS, which are primarily produced in mitochondria.[185] Notably, hyperphosphorylated Tau exacerbates mitochondrial damage by generating excessive ROS and promoting mitochondrial fission. Conversely, mitochondrial oxidative stress also promotes abnormal phosphorylation and

Table 2 Mitochondria-Targeted Nanosystems in CNS Disorders

Category	Classification	Representive Nanosystems	Mito-Targeting Strategies	Active Drugs/Cores	Effect of the Nanosystems Treatment on Mitochondrial Function	Reference
AD	Organic nanosystems	Curcumin-loaded red blood cell membrane-camouflaged human serum albumin nanoparticles bearing T807 and TPP molecules (CUR-loaded T807/TPP-RBC-NPs)	TPP	Curcumin	• Not only penetrate the BBB but also target nerve cells, and further localize in the mitochondria • Mitigate mitochondrial oxidative stress • Suppress neuronal death	[149]
		Co-decoration with neural cell adhesion molecule (NCAM) mimetic peptide C3 and TPP and encapsulated with resveratrol (CT-NM/Res)	TPP	Resveratrol	• Scavenge mitochondrial ROS • Rebalance mitochondrial fission and fusion • Decrease Aβ deposition and tau hyperphosphorylation,	[150]
		Loading resveratrol into red blood cell membrane-coated nanostructured lipid carriers bearing RVG29 and TPP (RVG/TPP-RSV NPs@RBCm)	TPP	Resveratrol	• Mitigate Aβ-related mitochondrial oxidative stress	[151]
		Genistein and macrophage membrane-encapsulated solid lipid nanoparticles attached with RVG29 and TPP (RVG/TPP-MASLNs-GS)	TPP	Genistein	• Scavenge mitochondrial ROS	[152]
		TPP-modified quercetin-derived smart nanomedicine (TQCN)	TPP	Quercetin	• Ameliorate iron overload-induced oxidative stress and mitochondrial dysfunction	[153]
		Conjugating lipophilic CsA and hydrophilic SS-31 through TK, and self-assembled into micelle in water (CsA-TK-SS-31, CTS)	TPP	CsA and SS-31	• Renovate the ultrastructure of damaged mitochondria • Restore the dynamic balance between mitochondrial fission and fusion • Enhance mitochondrial energy supply function	[98]
		Mitochondria-targeting fluorescent sensor (Mito-DDP)	Mito-DDP	/	• Viscosity visualization based on mitochondrial malfunction, inflammation, and AD models	[154]
	Inorganic nanosystems	TPP-conjugated 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino(polyethylene glycol)-2000]-functionalized molybdenum disulfide quantum dots (TPP-MoS_2)	TPP	MoS_2	• Target mitochondria in microglia • Scavenge ROS • Stimulate microglial polarization • Inhibit Aβ accumulation	[155]
		TPP-conjugated ceria nanoparticles (TPP-ceria NP)	TPP	Cyclic conversion between Ce^{3+} and Ce^{4+}	• Scavenge mitochondrial ROS efficiently to reduce oxidative stress	[156]
PD	Organic nanosystems	Artificial NVs loaded with Ursodeoxycholic acid (UDCA) further modifying with TPP (UDCA-NVs-TPP)	TPP	UDCA	• Reduce oxidative stress • Enhance ATP production	[157]
		Lycopene-loaded recombinant human H-ferritin (rHuHF) nanocages coupled with TPP (TPP-rHuHF-LYC)	TPP	Lycopene	• Scavenge mitochondrial ROS • Enhance mitochondrial energy metabolism • Boost PINK1/Parkin-mediated mitophagy	[158]
		$Cu_{2-x}Se$-based nanoparticles functionalized with curcumin and wrapped with DSPE-PEG_{2000}-TPP-modified macrophage membrane (CSCCT NPs)	TPP	Curcumin	• Scavenge mitochondrial ROS • Restore MMP • Protect the integrity of mitochondrial respiratory chain • Ameliorate mitochondrial dysfunction	[159]
		Neutrophil-like (HL-60) cell membrane and rabies virus glycoprotein-modified single-atom catalysts (RVG@AHM@Pt/CeO_2)	Electrostatic attraction	Pt/CeO_2	• Scavenge mitochondrial ROS • Induce mitophagy	[160]
		Incorporating RVG29 and deferoxamine into polydopamine-modified black phosphorus nanosheets (BDPR NSs)	Affinity-driven interaction	Deferoxamine	• Suppress ROS generation • Decrease mitochondrial iron accumulation	[161]
	Inorganic nanosystems	Microneedles loaded with mitochondrion-targeted liposome encapsulated iron (Fe)-isolated single-atom nanozymes (Mito@Fe-ISAzyme)	TPP	Fe-isolated single-atom nanozyme	• Scavenge ROS • Protect neurons	[162]

Glioma/ GBM	Organic nanosystems	Photosensitizer-loaded albumin nanoparticles with TPP modification (PS@chol-BSA NPs)	TPP	Photosensitizer	• Improve the efficacy of photodynamic therapy (PDT)	[163]
		Brain endothelial cell-derived extracellular vesicles with TPP-modified photosensitizer chlorin e6 (bEV (TPP-Ce6))	TPP	Photosensitizer chlorin e6	• ROS-induced apoptosis	[164]
		Glucose and TPP-modified and cascade-targeted liposomes (Lip-TPGS)	TPP	Doxorubicin prodrugs and chemotherapeutic sensitizer lonidamine	• Induce mitochondria dysfunction	[165]
		Doxorubicin-loaded liposomes with SS31 modification (LS-DOX)	SS-31	Doxorubicin	• Enhance cell uptake	[49]
		Cell-mitochondria hybrid membrane-modified nanoparticles loading Gboxin (HM-NPs)	Mitochondria membrane	Gboxin	• Mitochondria targeting • Induce mitochondria-mediated apoptosis	[59]
		TPP and 2,3-dimethylmaleic anhydride-conjugated glycol chitosan-Poly (lactic-*co*-glycolic acid) (GPTD) loaded with doxorubicin	TPP and pH-triggered charge-convertible moiety	Doxorubicin	• Efficiently accumulate into mitochondria	[166]
		$pGBEMA_{22}$-*b*-$pSSPPT_9$ (GBEPPT)	Enzyme-mediated charge-conversion	GBEPPT	• Disturb the homeostasis of mitochondria • Enhance the deep penetration via intracellular-to-intercellular delivery	[167]
		Lipid-small molecule hybrid nanoparticles (LPHNPs)	Mitochondria-targeting molecule	Pheophorbide a-quinolinium conjugate	• Induce severe mitochondrial dysfunction	[168]
		iRGD-conjugated oleanolic tertiary amine (iRGD-OTA NPs)	Tertiary amine modification	Lonidamine	• Interact with TOM70, resulting in cell death via pyroptosis	[169]
		Macrophage membrane-encapsulated black phosphorus nanosheets modified with TPP-conjugated lonidamine ($M@BP_{TLD}$)	TPP	Lonidamine	• Induce and reinforce pyroptosis via mitophagy flux blocking • Induce stronger mitochondrial oxidative stress	[170]
	Inorganic nanosystems	TPP-linked Chlorin e6 self-assembled with copper ions and thymopentin (TCe6@Cu/TP5 NPs)	TPP	Ce6 and Cu^{2+}	• PDT-mediated ROS accumulation and Cu^{2+} triggered cuproptosis	[171]
		Hypericin-conjugated gold nanoparticles (PEG-AuNPs@Hyp)	Mitochondria-targeting molecule	Hypericin	• Trigger oxidative stress	[172]
		Carbon dots based on metformin and Gallic acid (MGA-CDs)	Self-contained mitochondrial targeting ability	/	• Disturb the glycerophospholipid metabolism pathway by inhibiting the expression of PLPP4 • Induce ferroptosis	[173]
Ischemic stroke	Organic nanosystems	ROS-responsiveness and mitochondrial-targeted nanoparticles (SPNPs)	SS-31	ROS-responsive skeleton and SS-31	• Alleviate oxidative stress • Diminish inflammation • Repair mitochondrial function • Decrease apoptosis	[107]
		SS31-hyaluronic acid-quercetin (SS31-HA-QT)	SS31	Quercetin and SS31	• Exert neuron-protection by activating mitophagy	[50]
		Resveratrol-loaded Poly(ethylene glycol)-acetal-polycaprolactone-poly(ethylene glycol) modified with cRGD and TPP (cRGD/TPP@Res)	TPP	Resveratrol	• Scavenge ROS • Alleviate oxidative stress and inflammation	[174]
	Inorganic nanosystems	TPP-modified ceria nanoenzymes and roflumilast (TPP@(CeO_2+ROF))	TPP	Roflumilast and ceria	• Scavenge ROS • Regulate mitochondrial function • Anti-inflammatory	[175]
		Magnetic field driven and mitochondria-targeted ceria nanosystem (MMTCe)	TPP	Cyclic conversion between Ce^{3+} and Ce^{4+}	• Scavenge ROS • Reduce oxidative stress • Rebalance the ischemic microenvironment	[176]
TBI	Organic nanosystems	TPP and N-Acetyl cysteine-modified hydroxyl PAMAM dendrimer-drug construct (TPP-D-NAC)	TPP	N-Acetyl cysteine	• Attenuate oxidative stress	[177]
		Red blood cell-coated nanostructured lipid carriers loaded with PARP inhibitor olaparib and modified with C3 and SS31 peptide (C3/SS31-RBCNLCs)	SS-31	Olaparib	• Improve mitochondrial function • Reduce neuronal death	[178]
Others	Inorganic nanosystems	Luminescent AuAg nanoclusters-based probe conjugated with TPP	TPP	/	• Target to mitochondria • Brain imaging	[179]

https://doi.org/10.2147/IJN.S562666

aggregation of Tau protein.[186] Hence, targeting mitochondria and alleviating mitochondrial dysfunction are critical strategies for treating AD.

Various mitochondria-targeted nanosystems have been employed in AD treatment, designed with mitochondria-targeting peptides (such as TPP and SS-31) and loaded with therapeutic agents (eg, curcumin, resveratrol, methylene blue, etc).[149–153,155,186] Ceria (CeO_2) nanoparticles, widely studied for their potential ROS-scavenging activity through shuttling between Ce^{3+} and Ce^{4+} oxidation states, have been modified to target mitochondria. Kwon et al designed TPP-conjugated CeO_2 nanoparticles (TPP-ceria NPs) that could specifically target mitochondria and suppress neuronal death in an AD mouse model.[156] After TPP modification, significantly higher mitochondrial localization was observed in SH-SY5Y cells treated with FITC-TPP-ceria NPs compared to FITC-ceria NPs. Moreover, TPP-ceria NPs markedly inhibited Aβ-induced mitochondrial ROS production and reduced reactive gliosis and morphological mitochondrial damage, demonstrating that mitochondrial therapeutics hold promise for AD treatment. Li et al have also utilized TPP to modify tetrahedral DNA framework-based nanoparticles (TDFNs) for mitochondria-targeting, as well as cholesterol for BBB crossing and antisense oligonucleotide (ASO) for diagnosis and gene silencing therapy of AD.[187] The results showed the efficient colocalization of TDFNs and MitoTracker Red in neuron cells, demonstrating the superior mitochondia-targeted ability of TDFNs.

In contrast to TPP, the SS-31 peptide not only targets neurons and mitochondria but also directly alleviates mitochondrial dysfunction and oxidative damage.[188] Specifically, SS-31 has shown beneficial effects in treating AD[189–191] and has been conjugated with cyclosporin A (CsA) via a TK bond (Figure 2).[98] The resulting self-assembled micelles (CsA-TK-SS-31, abbreviated as CTS) efficiently targeted the mitochondria of damaged neurons and microglia driven by SS-31. Upon exposure to high levels of ROS within mitochondria, the TK bond breaks, releasing CsA and SS-31. The CTS micelles demonstrated enhanced mitochondrial targeting ability and alleviated neuronal mitochondrial dysfunction and neuroinflammation in 5×FAD mice by restoring mitochondrial function and increasing anti-inflammatory cytokines.

Furthermore, mitochondrial targeted fluorescence probe (Mito-DDP) was also designed by Li et al.[154] The results of confocal images have demonstrated that Mito-DDP could effectively penetrate the membrane and target to mitochondria. Besides, this probe has the effect of viscosity sensing, including mitochondrial malfunction, cellular inflammation and AD models, providing a novel strategy for exploring the pathological role of viscosity in AD.

PD

PD, the second most common neurodegenerative disorder after AD, involves dopaminergic neuron degeneration and α-synuclein (α-syn) aggregation.[161] Mitochondrial dysfunction drives pathogenesis through impaired mitophagy and ROS overproduction.[192] Critically, α-syn accumulation induces cardiolipin exposure on the OMM, disrupting respiratory chain complexes, while mtROS promote α-syn oligomerization, forming a self-amplifying pathological loop.[193]

Based on the promising mitochondria-targeting properties of the TPP peptide in AD therapy, several studies have explored its use for PD treatment due to its efficient targeting capability. For example, Zhang et al constructed ursodeoxycholic acid (UDCA)-loaded macrophage-derived nanovesicles (NVs) modified with TPP (UDCA-NVs-TPP) to combat PD.[157] UDCA-NVs-TPP could efficiently target damaged neuronal mitochondria and restore mitochondrial dysfunction by mitigating oxidative stress, providing a promising therapeutic strategy for PD treatment. Additionally, TPP was utilized to confer mitochondria-targeting properties to an iron (Fe)-isolated single-atom nanozyme (Fe-ISAzyme) liposome (Mito@Fe-ISAzyme, MFeI).[162] Cells treated with MFeI showed higher enrichment in mitochondria compared to Fe-ISAzyme, increasing mitochondrial numbers and improving therapeutic outcomes. Furthermore, sequence-targeted nanodots (TPP-rHuHF-LYC) were created by loading lycopene into recombinant human H-ferritin (rHuHF) and coupling it with TPP as the mitochondria-targeting peptide.[158] TPP-rHuHF-LYC efficiently targeted neuronal mitochondria via receptor-mediated transcytosis at the BBB facilitated by rHuHF and the mitochondria-targeting ability of TPP. Results indicated that TPP-rHuHF-LYC could repair mitochondrial function by enhancing mitophagy and alleviate pathological deterioration, significantly improving the therapeutic efficiency for PD. Similarly, Zheng et al designed ultrasmall $Cu_{2-x}Se$ nanoparticles carrying curcumin, encapsulated within DSPE-PEG_{2000}-TPP-modified macrophage membranes (CSCCT NPs).[159] With focused ultrasound assistance and the targeting role of TPP,

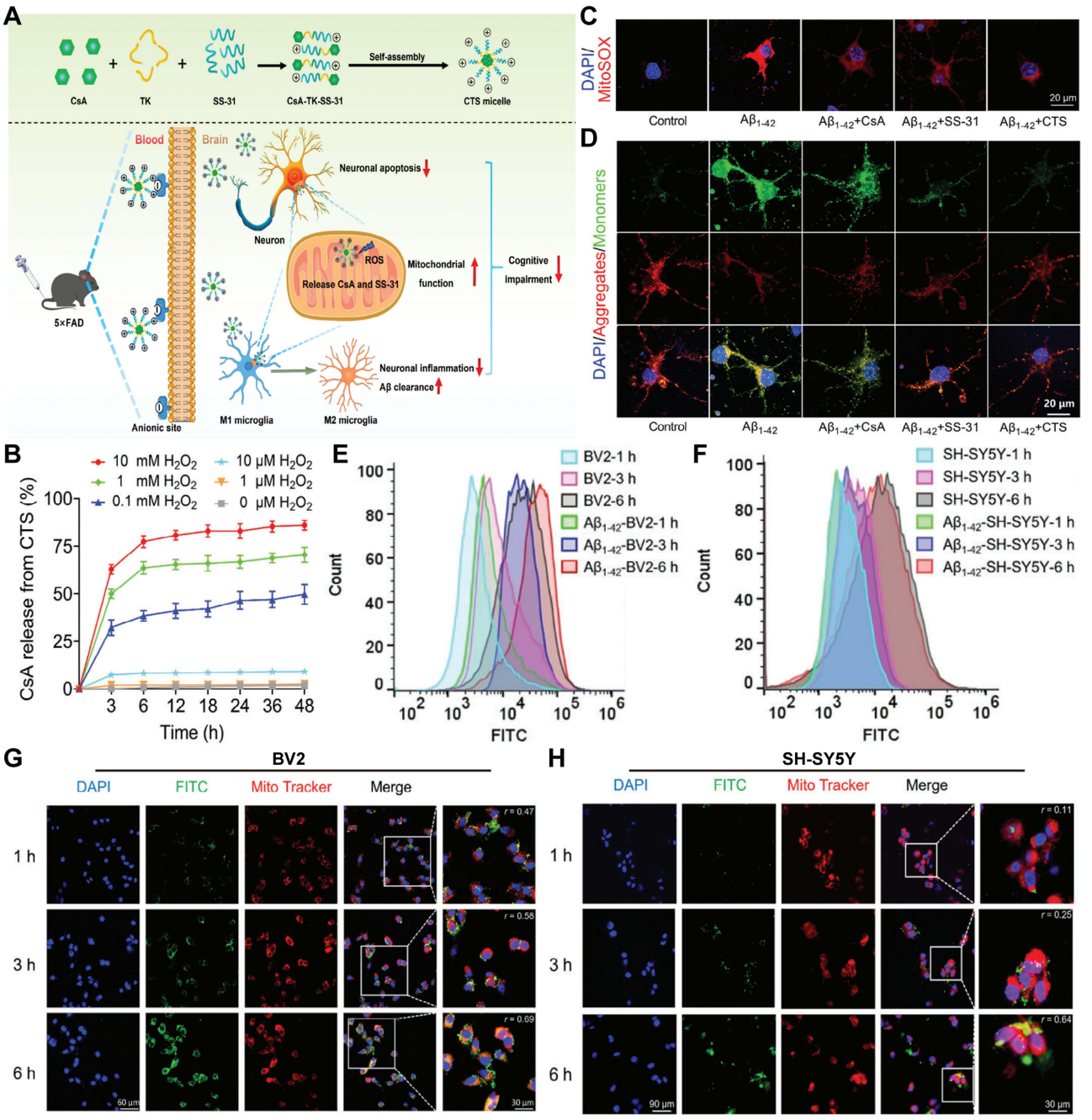


Figure 2 CTS micelle-based mitochondria-targeted nanosystems for AD. (**A**) Schematic illustration of the construction, targeting, and therapeutic mechanisms of CTS micelles for AD treatment. (**B**) Responsive release profile of CsA from CTS micelles. (**C**) Intracellular mitochondrial superoxide levels and (**D**) mitochondrial membrane potential following various treatments in Aβ1-42-damaged primary mouse neurons. Cellular uptake of FITC-labeled CTS (FITC@CTS) in both normal and Aβ1-42-damaged (**E**) BV2 or (**F**) SH-SY5Y cells as analyzed by flow cytometry. Confocal laser scanning microscopy (CLSM) images showing the colocalization of FITC@CTS with mitochondria in (**G**) BV2 or (**H**) SH-SY5Y cells. Reproduced with permission.[98] Copyright 2024, Wiley-VCH.

CSCCT NPs specifically targeted the mitochondria of inflammatory neurons, effectively scavenging mitochondrial ROS and promoting mitochondrial biogenesis, demonstrating a promising PD therapy strategy. Moreover, nanosystems without mitochondria-targeting peptide modifications have also shown effective mitochondrial targeting. Single-atom catalysts Pt/CeO_2 were developed for PD treatment by inducing autophagy.[160] After 4 h of Pt/CeO_2 treatment, mitochondria in mouse midbrain dopaminergic neuronal cells (MN9D) exhibited the highest colocalization coefficient with the nanomaterials, displaying a time-dependent increase. Interestingly, this colocalization decreased significantly from 0.692 to 0.347 when MN9D cells were pre-incubated with carbonyl cyanide m-chlorophenylhydrazone (CCCP),

https://doi.org/10.2147/IJN.S562666

which reduces mitochondrial membrane potential. These findings indicate that the mitochondria-targeting property of Pt/CeO_2 is mainly due to electrostatic attraction between the positively charged surface of Pt/CeO_2 and the negatively charged mitochondria. Furthermore, coating with a neutrophil membrane and modifying with RVG29 enabled RVG29@AHM@Pt/CeO_2 to cross the BBB effectively, break down mitochondrial ROS, and induce mitophagy for PD treatment, as well as improve the locomotor ability of PD mice (Figure 3).

In summary, mitochondria-targeted nanosystems represent promising strategies for treating neurodegenerative diseases through either mitochondria-targeting peptide modifications or the positive surface charge of nanosystems. Although positively charged nanosystems facilitate cellular uptake and permeability, their cytotoxicity and short blood

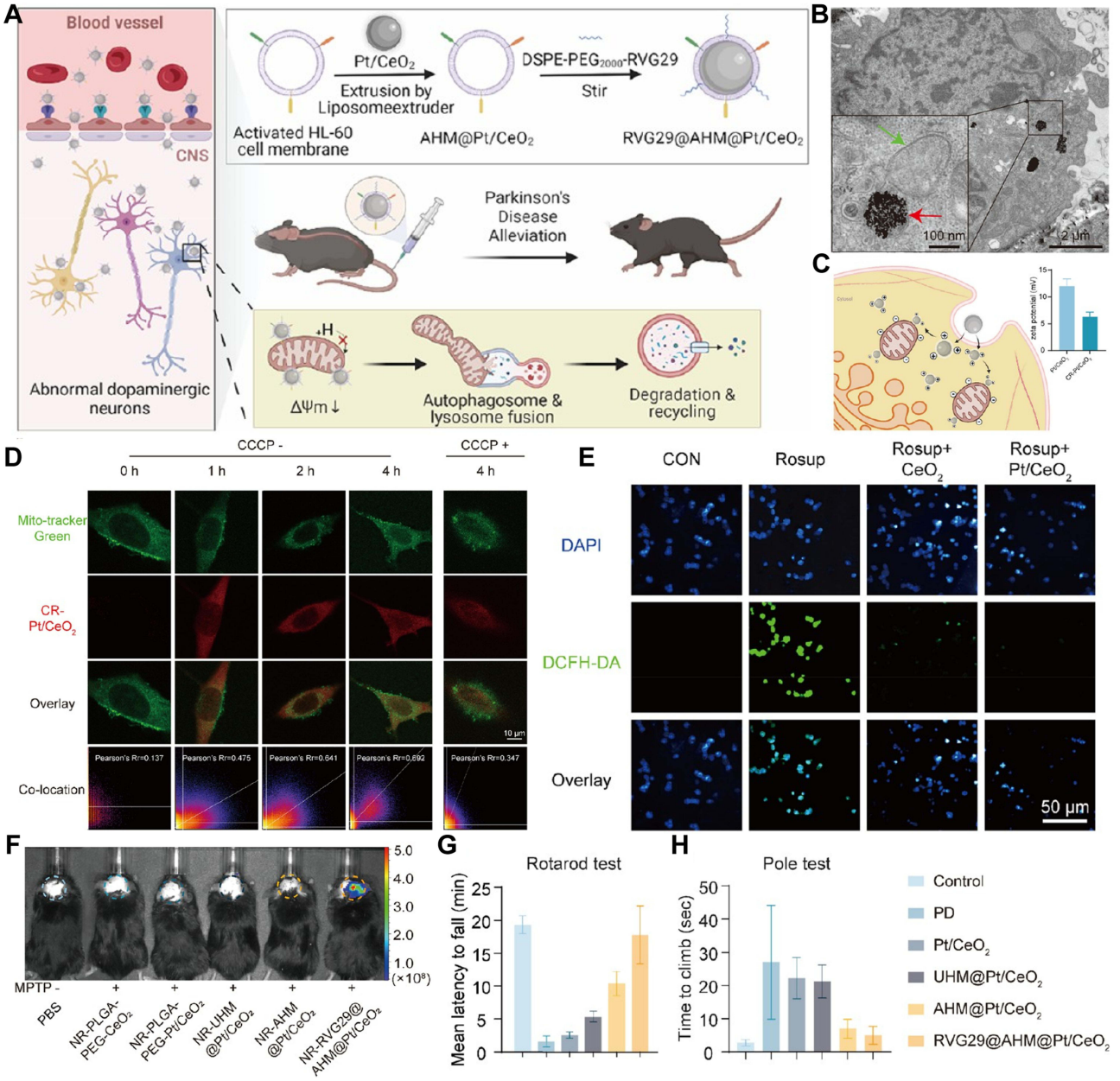


Figure 3 RVG29@AHM@Pt/CeO_2-based mitochondria-targeted nanosystems for PD. (**A**) Schematic illustration of the construction, targeting, and therapeutic mechanisms of RVG29@AHM@Pt/CeO_2 for PD treatment. (**B**) TEM image of cells after Pt/CeO_2 coincubation for 4 h. (**C**) Mechanism of Pt/CeO_2 targeting of mitochondria. (**D**) Mitochondria colocalization images of Pt/CeO_2 cultured with MN9D cells for 0, 1, 2 and 4 h. (**E**) ROS levels of cells. (**F**) Fluorescent images of the head of PD mice. (**G**) Latency to fall during the rotarod test of mice. (**H**) Delayed time to climb down during the pole test. Reproduced with permission.[160] Copyright 2023, American Chemical Society.

circulation times must be considered.[194,195] Further efforts should focus on enhancing the targeting capabilities and therapeutic outcomes of these nanosystems.

Brain Tumor

Due to the critical role of mitochondria in energy supply, cell differentiation, and growth, numerous therapeutic approaches have been designed to target mitochondria for precise tumor treatment by inducing mitochondrial dysfunction, such as decreasing ATP level, disrupting redox balance, depolarizing the mitochondrial membrane potential, interfering with ion homeostasis, and dysregulating mitophagy.[142] Hence, developing mitochondria-targeted nanosystems represents an effective strategy for cancer treatment by causing intrinsic apoptotic cell death.[196] Glioma, especially glioblastoma multiforme (GBM), is a malignant brain tumor characterized by rapid proliferation, high recurrence rates, and high mortality. Recently, mitochondria-targeted nanosystems have also been developed for the treatment of glioma or GBM, which can be achieved through mitochondria-targeted peptides or modifications of the mitochondrial cell membrane, as well as charge conversion.

Similar to their use in neurodegenerative diseases, TPP and SS-31 are commonly employed to endow nanosystems with mitochondria-targeting capabilities for brain tumor treatment. For instance, Kang et al constructed mitochondria-targeted photosensitizer-loaded albumin nanoparticles by conjugating (4-carboxy-butyl)-TPP with pheophorbide-a (PS@chol-BSA NPs) for targeting mitochondria in the treatment of malignant brain tumors.[163] TPP has also been linked to the photosensitizer Chlorin e6 (Ce6), self-assembled with drugs and ions, or encapsulated into brain endothelial cell-derived extracellular vesicles for enhanced brain penetration and mitochondria targeting, ultimately inducing mitochondrial impairment.[164,171] In addition, researchers have constructed nanosystems modified with mitochondria-targeted peptides for glioma/GBM treatment. Cascade-targeted liposomes (Lip-TPGS) were developed using glucose and TPP as targeting peptides.[165] Similarly, SS-31 was used to modify doxorubicin-loaded liposomes (LS-DOX) for BBB penetration and mitochondria targeting.[49]

As natural biomaterials, biomimetic nanomaterials based on nanovesicles and cell membranes have emerged as promising platforms for treating brain disorders due to their excellent biocompatibility and homologous-targeting ability.[197,198] Shi et al utilized GBM-cell membranes to camouflage nanoparticles for targeting homologous cancer cells, achieving remarkable targeting efficiency and anti-GBM efficacy.[199] Based on the unique advantages of GBM-cell membranes, Shi et al further developed a cancer cell-mitochondria hybrid membrane strategy for GBM treatment (Figure 4).[59] Compared to single cancer cell membranes, subcellular organelle-derived membranes can enhance the immune evasion capability of nanomaterials and be tailored for specific subcellular targeting. The results showed that hybrid membrane nanosystems (HM-NPs) had the highest overlap with mitochondria, indicating their superior mitochondria-targeting properties. After hybrid membrane coating, Gboxin could be effectively delivered to the mitochondria of cancer cells, interrupting ATP synthase function, leading to electron transport and energy metabolism disruption, ultimately causing mitochondria-mediated apoptosis.

Tumor microenvironment-triggered charge-convertible nanosystems have also been designed to enhance mitochondria uptake while reducing toxicity to normal cells. Jin et al reported pH-triggered charge-convertible micelles (GPTD) for glioma therapy.[166] By conjugating 2,3-dimethylmaleic anhydride to TPP-modified chitosan-poly (lactic-co-glycolic acid) polymers to form dimethyl maleic amides, these compounds convert from cationic to anionic via the transformation of amino groups to carboxyl groups in acidic microenvironments. Under the low pH conditions found in tumors, GPTD could efficiently accumulate in mitochondria following charge-mediated cellular internalization, subsequently releasing drugs to increase the anti-tumor effect. Additionally, Xiang et al designed a mitochondrion-disturbing nanosystem (GBEPPT) capable of enzyme-mediated charge conversion.[167] Once delivered to the tumor site where γ-glutamyl transpeptidase (GGT) is overexpressed, GBEPPT would reverse its surface charge from negative to positive. With the assistance of this positive charge, GBEPPT could easily target mitochondria to disrupt their homeostasis, resulting in enhanced deep penetration within GBM treatments.

Furthermore, some mitochondria-targeting molecules without additional targeting equipment, such as hypericin, pheophorbide a-quinolinium conjugate (PQC), and carbon dots modified with metformin and gallic acid (MGA-CDs), inherently localize to the mitochondria to trigger oxidative stress, induce severe mitochondrial dysfunction, or promote

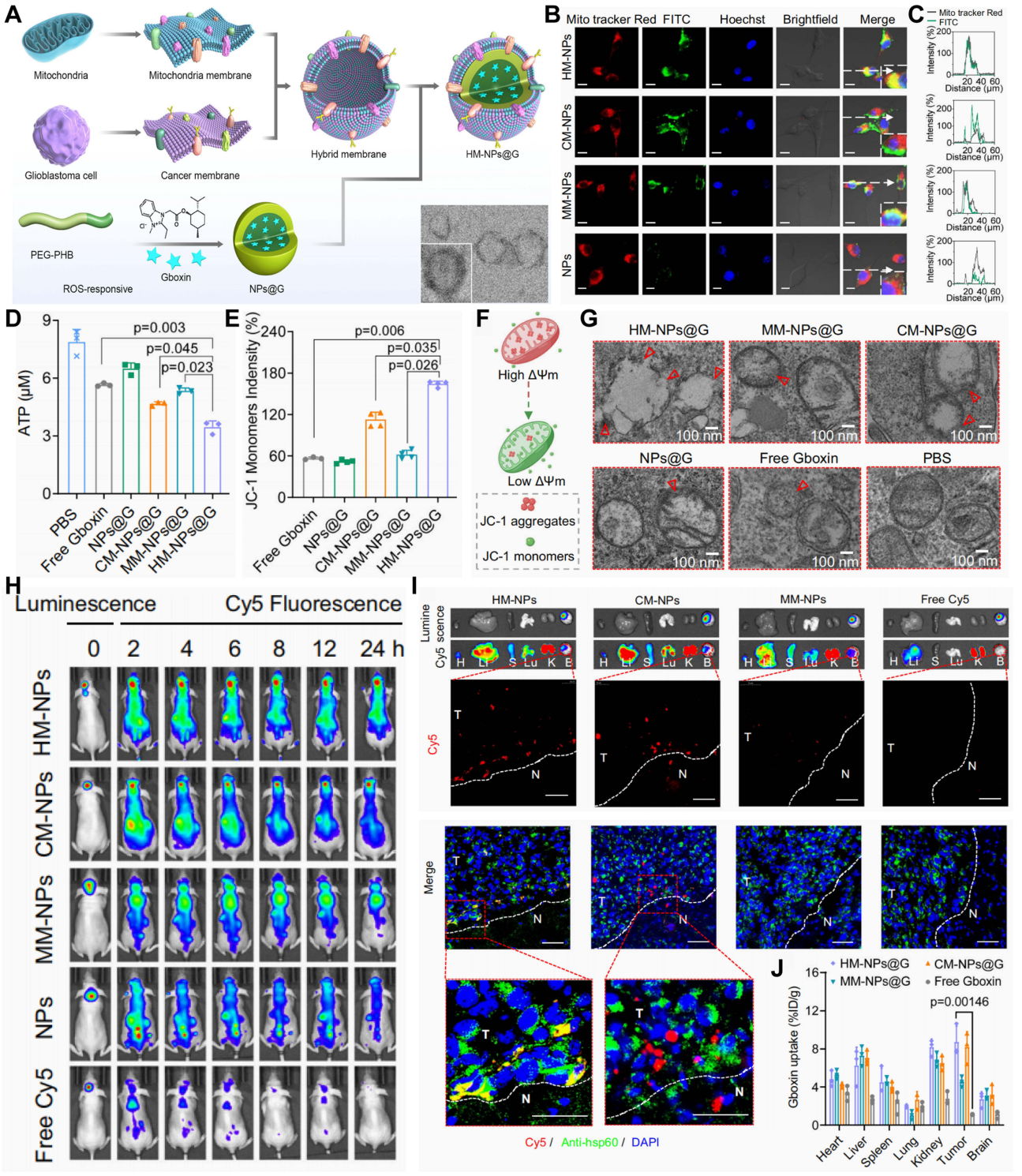


Figure 4 HM-NPs@G-based mitochondria-targeted nanosystems for brain tumor. (**A**) Schematic illustration of the preparation of HM-NPs@G. (**B**) CLSM images and (**C**) colocalization analysis of U87 cells after various nanosystems incubation. (**D**) ATP content of U87 cells after various treatments. (**E**) The fluorescence intensity of JC-1 monomer of U87 cells. (**F**) Schematic illustration of the changes of JC-1 structures with MMP. (**G**) TEM images of mitochondria after various treatments. (**H**) in vivo fluorescence images of U87-tumor bearing mice after Cy5-labeled nanosystems injection. (**I**) Ex vivo fluorescence images of Cy5 in major organs and brains, and the colocalization with mitochondria in GBM sites. (**J**) The Gboxin accumulation in major organs, tumors and brains. Reproduced with permission.[59] Copyright 2023, Springer Nature.

ferroptosis for GBM.[168,172,173] Recently, a novel mitochondria-targeting strategy was demonstrated by Gao et al.[169] They found that tertiary amine modification could confer triterpene nanoparticles (eg, oleanolic acid, lupeol, and glycyrrhetinic acid) with mitochondria-targeting properties, enabling effective GBM treatment through pyroptosis after interaction with the translocase of the outer mitochondrial membrane 70 (TOM70).

Collectively, mitochondria-targeting strategies represent a promising avenue for brain tumor treatment by generating excessive ROS, triggering oxidative stress, and exacerbating mitochondrial dysfunction. Through the use of mitochondria-targeted peptides or membrane modifications, microenvironment-responsive charge conversion, and leveraging their inherent natural properties, nanosystems can effectively target the mitochondria of tumor cells and exert their functions therein.

Ischemic Stroke

Ischemic stroke has become a prevalent neurological disorder globally, characterized by high mortality and disability rates. Following ischemic injury, mitochondrial function is compromised under hypoxic or ischemic conditions, leading to oxidative stress, microglial activation, inflammation, and ultimately neuronal cell death.[200] Targeting mitochondria can directly modulate cellular metabolism, thereby maximizing therapeutic outcomes while minimizing toxicity. The overproduction of ROS by damaged mitochondria plays a critical role in ischemic stroke injury. Therefore, strategies aimed at targeting mitochondria represent promising approaches for mitigating ischemic stroke damage.

Similar to neurodegenerative diseases and brain tumors, TPP and SS-31 are common mitochondria-targeted modification strategies used in ischemic stroke.[50,107] For instance, Wang et al proposed a stepwise targeting nanoplatform by modified pH-responsive micelles with cRGD and TPP peptide (cRGD/TPP@Res) for brain-mitochondria targeting.[174] Upon entering ischemic tissues with an acidic environment, the PEG shell detaches from the micelles due to the breakage of acetal bonds, followed by exposing TPP for mitochondria targeting. Resveratrol accumulates within the mitochondria, effectively scavenging ROS and alleviating oxidative stress and inflammation.

Ceria nanoenzymes (CeNZs) have garnered attention due to their excellent ROS scavenging capabilities and reversible conversion properties.[201,202] Liao et al developed a mitochondria-targeted nanosystem based on CeNZs and incorporated roflumilast for synergistic treatment of ischemic stroke (Figure 5A–5D).[175] After TPP-targeted modification, TPP@(CeO_2+ROF) nanosystems were rapidly taken up by neuronal cells within 1.5 h, exhibiting higher co-localization with mitochondria compared to non-targeting nanosystems. Additionally, TPP@(CeO_2+ROF) exhibited effective ROS scavenging, mitochondrial function regulation, and anti-inflammatory properties, demonstrating comprehensive treatment of ischemic stroke. To improve the brain-targeting ability of nanosystems, they further developed a magnetic field-driven and mitochondria-targeting ceria nanosystem (MMTCe) by anchoring TPP-Ce nanoparticles coated with BV2 cell membranes to maleimide-functionalized superparamagnetic iron oxide nanoparticles (Figure 5E–5H).[176] Under external magnetic field guidance, MMTCe efficiently reached the brain and targeted damaged mitochondria with the assistance of TPP. Subsequently, MMTCe exerted its therapeutic efficiency by scavenging ROS, reducing oxidative stress, thereby rebalancing the ischemic microenvironment. This study presented a magnetically driven, mitochondria-targeted nanosystem, providing a multifaceted approach for ischemic stroke treatment.

Mitochondrial dysfunction plays a significant role in the pathogenesis of ischemic stroke, impairing energy supply, exacerbating oxidative stress, and causing neuronal death. Hence, restoring mitochondrial functions is essential in treating ischemic stroke. Researchers have recently employed mitochondria-targeted peptides, including TPP and SS-31, to modify nanosystems for scavenging ROS, alleviating inflammation, and promoting mitophagy. Further investigations should focus on mitochondrial biology and specific molecular mechanisms, which will facilitate the development of novel mitochondria-targeted approaches in ischemic stroke treatment.

Others

Similar to acute central nervous system injuries and neurodegenerative diseases, mitochondrial dysfunction also plays an essential role in other brain disorders, such as traumatic brain injury (TBI), cognitive deficits, and neuropathy.[203,204] Neurological functions are impaired by changes in mitochondria resulting from increased ROS production and decreased

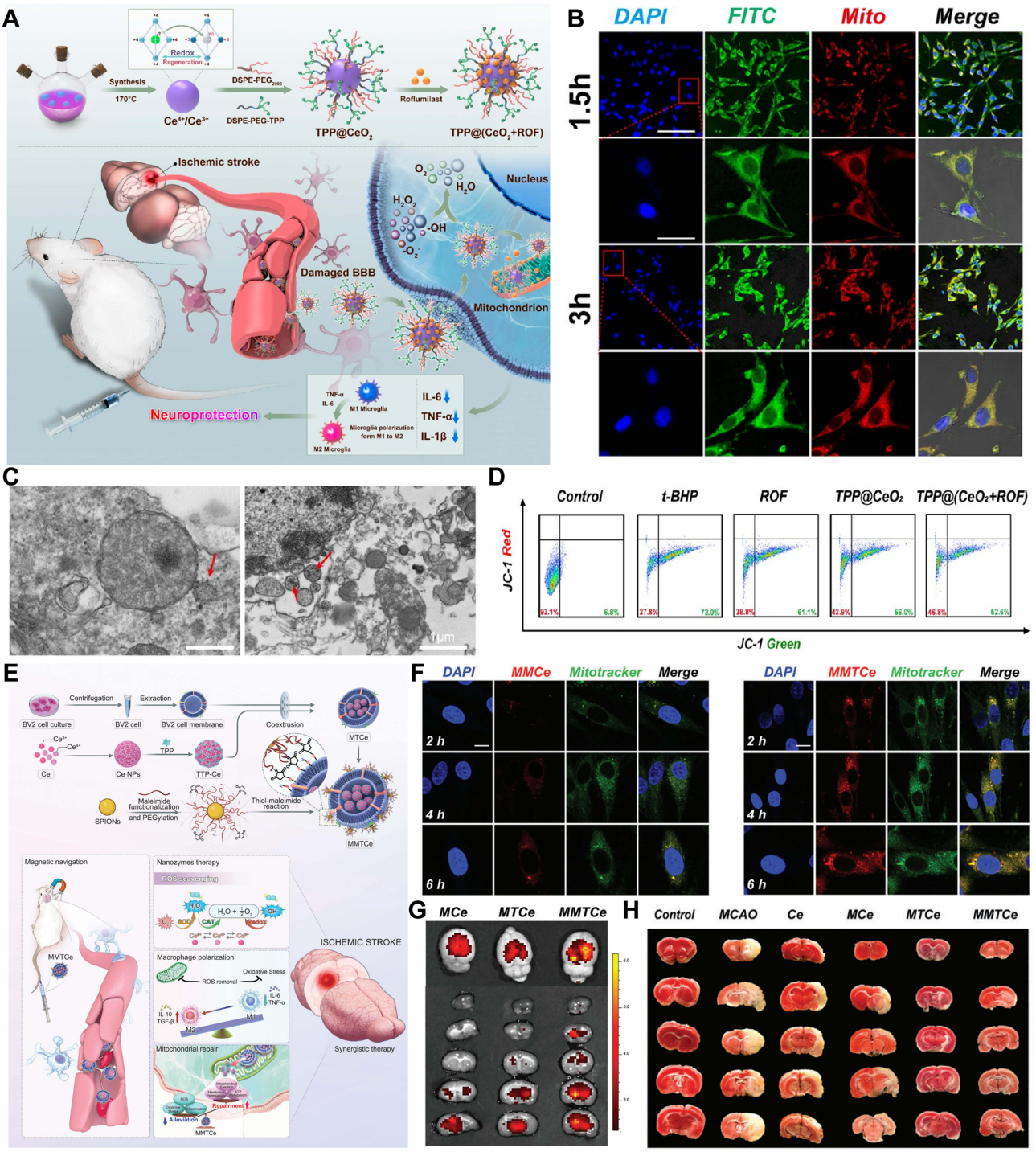


Figure 5 Ce-based mitochondria-targeted nanosystems for ischemic stroke. (**A**) Schematic illustration of the construction, mitochondria-targeting, and therapeutic effects of TPP@(CeO_2+ROF). (**B**) Co-localization of nanosystems with mitochondria in PC12 cells. (**C**) TEM images of TPP@(CeO_2+ROF) in mitochondria of PC12 cells. (**D**) JC-1 fluorescence analyzed by flow cytometry. Reproduced with permission.[175] Copyright 2024, American Chemical Society. (**E**) Schematic representation of the preparation of MMTCe nanosystems and their neuroprotective effects. (**F**) CLSM images of mitochondria-targeted ability of DiR-labeled MMCe and MMTCe. (**G**) Ex vivo fluorescence images of brain and section from rats after various treatments. (**H**) The cerebral infarct volume using TTC staining. Reproduced with permission.[176] Copyright 2025, Wiley-VCH.

energy supply. Therefore, proposing potential therapeutic approaches for reversing mitochondrial dysfunction is crucial for the treatment of brain diseases.

TBI is a complex and biphasic condition. The initial phase involves direct tissue damage, while the secondary phase is characterized by calcium overload, excessive ROS production, and inflammation.[205] Mitochondrial dysfunction frequently occurs during this secondary phase. Consequently, mitochondria represent a promising target for intervention in TBI. Researchers have developed mitochondria-targeted nanosystems for managing TBI. For instance, Sharma et al utilized polyamidoamine dendrimers to encapsulate N-acetyl cysteine (NAC), which acts as an antioxidant.[177] After being modified with TPP, the NAC was specifically targeted to the mitochondria in injured glial cells. This approach significantly reduced oxidative stress both in vitro using cell models and in vivo using rabbit TBI models, demonstrating that mitochondria-targeted strategies could enhance therapeutic efficacy in TBI.

Furthermore, Sun et al introduced a biomimetic nanosystem co-modified with C3 peptides and SS31 (C3/SS31-RBCNLCs) for targeting neuronal mitochondria in the brain.[178] Both in vitro and in vivo experiments showed that the encapsulated drug olaparib could be efficiently delivered into brain mitochondria, thereby improving mitochondrial function, reducing neuronal death, and delaying the pathological progression of TBI. Besides, various fluorescence probes were also constructed by researchers to realize mitochondria-targeting and brain imaging. For instance, Pan et al proposed a ligand engineering of luminescent AuAg nanoclusters conjugated with TPP on the surface.[179] In vitro cell experiments have revealed that AuAg NCs@TPP probe could effectively target to the mitochondria of 4T1 and BV2 cells, exhibiting outstanding mitochondria-targeted property.

Conclusion and Perspective

Mitochondria, as central orchestrators of cellular energetics, calcium homeostasis, and apoptotic signaling, represent pivotal therapeutic targets for CNS disorders. Mounting evidence implicates mitochondrial dysfunction as a convergent pathological mechanism underpinning neurodegenerative diseases (eg, AD, PD), brain tumors, ischemic stroke, and TBI. Consequently, strategies aimed at restoring mitochondrial homeostasis hold transformative potential for CNS therapeutics. Mitochondria-targeted nanosystems have emerged as a paradigm-shifting approach, enabling spatiotemporally precise delivery of therapeutic cargo to rescue mitochondrial function and amplify treatment efficacy.

This review has delineated the rational design principles and expanding therapeutic applications of mitochondria-targeted nanosystems. Key targeting modalities—including cationic molecules, mitochondrial-penetrating peptides, and bioengineered mitochondrial membranes—demonstrate markedly enhanced mitochondrial accumulation and intervention capacity. We further synthesized recent advances in deploying these nanosystems across diverse CNS pathologies (including AD, PD, glioma, ischemic stroke, and TBI etc)., highlighting their roles in mitigating oxidative stress, modulating mitophagy, and promoting mitochondrial biogenesis to achieve superior therapeutic outcomes. Despite these promising advances, critical challenges demand resolution before clinical translation (Figure 6).

To date, mitochondria-targeted nanosystems have yet to be employed in clinical studies, potentially due to challenges related to their complex preparation, reproducibility, and metabolism. Consequently, greater emphasis should be placed on the thorough investigation of the physicochemical characterization of these nanosystems. Moreover, before these systems can advance to preclinical trials, it is essential to evaluate their in vivo stability, long-term effects, and metabolic pathways. Addressing these aspects will be crucial for translating mitochondria-targeted nanosystems from experimental models to potential clinical applications.

Size, shape, and charge play essential roles in determining the biological fate of nanosystems, which influence their in vivo cellular uptake and circulation lifetime.[206,207] For example, nanosystems with over 200 nm size have poor penetration and cell interaction properties. In contrast, nanosystems with small size can enhance the penetration, but are rapidly cleared from the systems by kidneys during the in vivo circulation.[208] As for the charge of nanosystems, the cationic charge of nanosystems improves cellular uptake efficiency, which is mainly attributed to the negative charge of cell membrane, but it is also associated with cytotoxicity. For instance, the inherent cationic charge of common mitochondrial ligands (eg, TPP) raises concerns regarding membrane perturbation and off-target cytotoxicity. Hence, future research must prioritize rigorous toxicological profiling of nanosystems across relevant cell types and disease

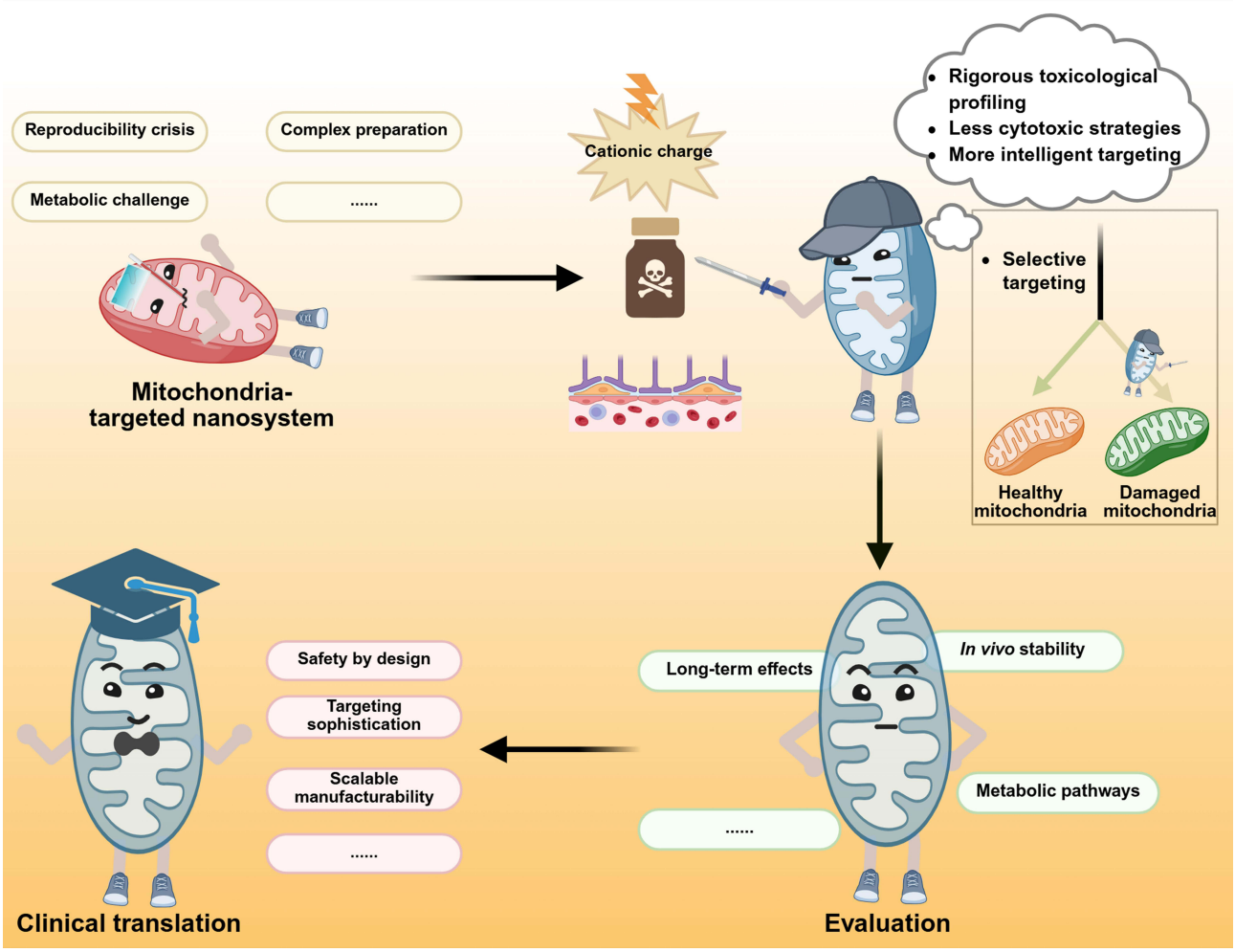


Figure 6 Current challenges and future prospects of mitochondria-targeted nanosystems. Created with BioRender.com.

models, coupled with the development of less cytotoxic strategies such as coating with biomimetic mitochondrial membranes and engineering delivery systems with targeted ligands.

Effective CNS delivery necessitates sequential navigation of formidable obstacles: the BBB, the complex brain parenchyma, and ultimately, the mitochondrial double membranes. Furthermore, in order to enhance the accumulation of nanosystems in the mitochondria of specific cell types, various sub-organelle targeting strategies have been developed in combination with mitochondria-targeted approaches. For instance, T807 and TPP peptides were co-functionalized to red blood cell-modified nanosystems by Gao et al, which could not only penetrate the BBB but also target neuronal mitochondria.[149] The similar functions could also be observed by RVG29 peptide modification.[152] While dual-targeting strategies (eg, conjugating BBB-penetrating ligands like transferrin or angiopep-2 with mitochondrial homing signals like SS-31) show promise, their efficiency remains limited. A concerted effort is required to engineer next-generation ligands with enhanced specificity, avidity, and stimuli-responsiveness for both brain entry and mitochondrial localization, thereby minimizing systemic exposure and maximizing the therapeutic index.

A fundamental limitation of current platforms is their inability to distinguish pathologically damaged mitochondria from functional counterparts. Cellular homeostasis relies on mitochondrial quality control mechanisms: damaged organelles (exhibiting fragmentation, depolarized membrane potential, and proteotoxic/oxidative stress) are segregated via fission and targeted for mitophagy, while healthy units sustain essential functions. Indiscriminate nanocarrier accumulation in all mitochondria poses potential risks. Delivery of cytotoxic payloads or nanomaterial-induced stress to healthy mitochondria could irreversibly compromise cellular viability. Next-generation systems demand molecular

intelligence for damaged mitochondrial targeting, such as energy-state-responsive delivery, damage marker-guided binding, or ROS/protease-activatable systems.

In summary, subcellular targeting strategies, including but not limited to mitochondrial-targeted nanosystems, offer promising approaches for treating CNS diseases. Future success hinges on prioritizing safety by design, enhancing targeting sophistication, and demonstrating scalable manufacturability, paving the way for these potent nanoscale interventions to transform the treatment landscape for devastating neurological diseases.

Data Sharing Statement

No data was used for the research described in the article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Conceptualization: Y.Z., X.C. and X.Z.; literature curation: X.Z., J.C. and B.W., writing – original draft: X.Z., J.C., B.W. and X.C.; writing—review and editing: Y.Z. and X.C.; supervision: Y.Z. All authors read and approved the final manuscript.

Funding

This work was supported by grants from the National Natural Science Foundation of China (82473900, 82273903), Zhejiang Provincial Natural Science Foundation (LD25H090002), and Research Project of Zhejiang Chinese Medical University (2025JKZKTS33).

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

References

1. Li Y, Zhang H, Yu C, et al. New insights into mitochondria in health and diseases. *Int J Mol Sci*. 2024;25(18). doi:10.3390/ijms25189975
2. Bruce Alberts AJ, Lewis J, Raff M, Roberts K, Walter P. *Molecular Biology of the Cell*. 4th ed. 2002.
3. Koranteng J, Chung KF, Michaeloudes C, Bhavsar P. The role of mitochondria in eosinophil function: implications for severe asthma pathogenesis. *Front Cell Dev Biol*. 2024;12:1360079. doi:10.3389/fcell.2024.1360079
4. Hatefi Y. The mitochondrial electron transport and oxidative phosphorylation system. *Annu Rev Biochem*. 1985;54:1015–1069. doi:10.1146/annurev.bi.54.070185.005055
5. Galluzzi L, Kepp O, Trojel-Hansen C, Kroemer G. Mitochondrial control of cellular life, stress, and death. *Circ Res*. 2012;111(9):1198–1207. doi:10.1161/circresaha.112.268946
6. Roger AJ, Muñoz-Gómez SA, Kamikawa R. The origin and diversification of mitochondria. *Curr Biol*. 2017;27(21):R1177–r1192. doi:10.1016/j.cub.2017.09.015
7. Bonora M, Giorgi C, Pinton P. Molecular mechanisms and consequences of mitochondrial permeability transition. *Nat Rev Mol Cell Biol*. 2022;23(4):266–285. doi:10.1038/s41580-021-00433-y
8. Zhou C, Kuang M, Tao Y, et al. Nynrin preserves hematopoietic stem cell function by inhibiting the mitochondrial permeability transition pore opening. *Cell Stem Cell*. 2024;31(9):1359–1375.e8. doi:10.1016/j.stem.2024.06.007
9. Nunnari J, Suomalainen A. Mitochondria: in sickness and in health. *Cell*. 2012;148(6):1145–1159. doi:10.1016/j.cell.2012.02.035
10. GBD 2019 Collaborators. Global mortality from dementia: application of a new method and results from the Global Burden of Disease Study 2019. *Alzheimers Dement*. 2021;7(1):e12200. doi:10.1002/trc2.12200
11. GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18(5):459–480. doi:10.1016/s1474-4422(18)30499-x
12. Rong L, Li N, Zhang Z. Emerging therapies for glioblastoma: current state and future directions. *J Exp Clin Cancer Res*. 2022;41(1):142. doi:10.1186/s13046-022-02349-7
13. Hirai K, Aliev G, Nunomura A, et al. Mitochondrial abnormalities in Alzheimer's disease. *J Neurosci*. 2001;21(9):3017–3023. doi:10.1523/jneurosci.21-09-03017.2001
14. Swerdlow RH. Mitochondria and Mitochondrial Cascades in Alzheimer's Disease. *J Alzheimers Dis*. 2018;62(3):1403–1416. doi:10.3233/jad-170585
15. Rostagno AA. Pathogenesis of Alzheimer's disease. *Int J Mol Sci*. 2022;24(1). doi:10.3390/ijms24010107

16. Schapira AH, Cooper JM, Dexter D, Clark JB, Jenner P, Marsden CD. Mitochondrial complex I deficiency in Parkinson's disease. *J Neurochem*. 1990;54(3):823–827. doi:10.1111/j.1471-4159.1990.tb02325.x
17. Yang P, Shuai W, Wang X, et al. Mitophagy in neurodegenerative diseases: mechanisms of action and the advances of drug discovery. *J Med Chem*. 2025;68(4):3970–3994. doi:10.1021/acs.jmedchem.4c01779
18. Kalogeris T, Bao Y, Korthuis RJ. Mitochondrial reactive oxygen species: a double edged sword in ischemia/reperfusion vs preconditioning. *Redox Biol*. 2014;2:702–714. doi:10.1016/j.redox.2014.05.006
19. He Z, Ning N, Zhou Q, Khoshnam SE, Farzaneh M. Mitochondria as a therapeutic target for ischemic stroke. *Free Radic Biol Med*. 2020;146:45–58. doi:10.1016/j.freeradbiomed.2019.11.005
20. Huang L, Huang XH, Yang X, et al. Novel nano-drug delivery system for natural products and their application. *Pharmacol Res*. 2024;201:107100. doi:10.1016/j.phrs.2024.107100
21. Lv Y, Li W, Liao W, et al. Nano-drug delivery systems based on natural products. *Int J Nanomed*. 2024;19:541–569. doi:10.2147/ijn.S443692
22. Pardridge WM. Blood-brain barrier delivery. *Drug Discov Today*. 2007;12(1–2):54–61. doi:10.1016/j.drudis.2006.10.013
23. Saraiva C, Praça C, Ferreira R, Santos T, Ferreira L, Bernardino L. Nanoparticle-mediated brain drug delivery: overcoming blood-brain barrier to treat neurodegenerative diseases. *J Control Release*. 2016;235:34–47. doi:10.1016/j.jconrel.2016.05.044
24. Gao X, Xu J, Yao T, Liu X, Zhang H, Zhan C. Peptide-decorated nanocarriers penetrating the blood-brain barrier for imaging and therapy of brain diseases. *Adv Drug Deliv Rev*. 2022;187:114362. doi:10.1016/j.addr.2022.114362
25. Wu D, Chen Q, Chen X, Han F, Chen Z, Wang Y. The blood-brain barrier: structure, regulation, and drug delivery. *Signal Transduct Target Ther*. 2023;8(1):217. doi:10.1038/s41392-023-01481-w
26. Khan T, Waseem R, Zehra Z, et al. Mitochondrial dysfunction: pathophysiology and mitochondria-targeted drug delivery approaches. *Pharmaceutics*. 2022;14(12). doi:10.3390/pharmaceutics14122657
27. Wang Z, Guo W, Kuang X, Hou S, Liu H. Nanopreparations for mitochondria targeting drug delivery system: current strategies and future prospective. *Asian J Pharm Sci*. 2017;12(6):498–508. doi:10.1016/j.ajps.2017.05.006
28. Chen Z, Chen L, Lyu TD, et al. Targeted mitochondrial nanomaterials in biomedicine: advances in therapeutic strategies and imaging modalities. *Acta Biomater*. 2024;186:1–29. doi:10.1016/j.actbio.2024.08.008
29. Zhao M, Wang J, Zhu S, et al. Mitochondrion-based organellar therapies for central nervous system diseases. *Cell Commun Signal*. 2024;22 (1):487. doi:10.1186/s12964-024-01843-z
30. Huang C, Deng K, Wu M. Mitochondrial cristae in health and disease. *Int J Biol Macromol*. 2023;235:123755. doi:10.1016/j.ijbiomac.2023.123755
31. Palikaras K, Lionaki E, Tavernarakis N. Mechanisms of mitophagy in cellular homeostasis, physiology and pathology. *Nat Cell Biol*. 2018;20 (9):1013–1022. doi:10.1038/s41556-018-0176-2
32. Zielonka J, Joseph J, Sikora A, et al. Mitochondria-targeted triphenylphosphonium-based compounds: syntheses, mechanisms of action, and therapeutic and diagnostic applications. *Chem Rev*. 2017;117(15):10043–10120. doi:10.1021/acs.chemrev.7b00042
33. Zhou L, Du Y, Shang Y, Xiang D, Xia X. A novel triptolide nano-liposome with mitochondrial targeting for treatment of hepatocellular carcinoma. *Int J Nanomed*. 2024;19:12975–12998. doi:10.2147/ijn.S498099
34. Li WQ, Wu JY, Xiang DX, et al. Micelles loaded with puerarin and modified with triphenylphosphonium cation possess mitochondrial targeting and demonstrate enhanced protective effect against isoprenaline-induced H9c2 cells apoptosis. *Int J Nanomed*. 2019;14:8345–8360. doi:10.2147/ijn.S219670
35. Cheng X, Xia T, Han M, et al. Mitochondria-targeting bimetallic cluster nanozymes alleviate neuropathic pain through scavenging ROS and reducing inflammation. *Adv Healthc Mater*. 2025;14(8):e2401607. doi:10.1002/adhm.202401607
36. Heise N, Becker S, Mueller T, Bache M, Csuk R, Güttler A. Mitochondria-targeting 1,5-Diazacyclooctane-Spacered Triterpene rhodamine conjugates exhibit cytotoxicity at sub-nanomolar concentration against breast cancer cells. *Int J Mol Sci*. 2023;24(13). doi:10.3390/ijms241310695
37. Biswas S, Dodwadkar NS, Sawant RR, Koshkaryev A, Torchilin VP. Surface modification of liposomes with rhodamine-123-conjugated polymer results in enhanced mitochondrial targeting. *J Drug Target*. 2011;19(7):552–561. doi:10.3109/1061186x.2010.536983
38. Johnson LV, Walsh ML, Chen LB. Localization of mitochondria in living cells with rhodamine 123. *Proc Natl Acad Sci U S A*. 1980;77(2):990–994. doi:10.1073/pnas.77.2.990
39. Murphy MP. Selective targeting of bioactive compounds to mitochondria. *Trends Biotechnol*. 1997;15(8):326–330. doi:10.1016/s0167-7799(97)01068-8
40. Bergmans JMM, van de Westerlo EMA, Grefte S, Adjobo-Hermans MJW, Koopman WJH. Mitochondrial morphofunctional profiling in primary human skin fibroblasts using TMRM and mitotracker green co-staining. *Methods Mol Biol*. 2025;2878:223–232. doi:10.1007/978-1-0716-4264-1_12
41. Xing W, Liu G, Zhang Y, Zhang T, Lou H, Fan P. Selective antitumor effect and lower toxicity of mitochondrion-targeting derivatization of triptolide. *J Med Chem*. 2024;67(2):1093–1114. doi:10.1021/acs.jmedchem.3c01508
42. Chen H, Wang J, Feng X, et al. Mitochondria-targeting fluorescent molecules for high efficiency cancer growth inhibition and imaging. *Chem Sci*. 2019;10(34):7946–7951. doi:10.1039/c9sc01410a
43. Li Y, Li XM, Wei LS, Ye JF. Advancements in mitochondrial-targeted nanotherapeutics: overcoming biological obstacles and optimizing drug delivery. *Front Immunol*. 2024;15:1451989. doi:10.3389/fimmu.2024.1451989
44. Weiss MJ, Wong JR, Ha CS, et al. Dequalinium, a topical antimicrobial agent, displays anticarcinoma activity based on selective mitochondrial accumulation. *Proc Natl Acad Sci U S A*. 1987;84(15):5444–5448. doi:10.1073/pnas.84.15.5444
45. Smith RA, Murphy MP. Animal and human studies with the mitochondria-targeted antioxidant MitoQ. *Ann N Y Acad Sci*. 2010;1201:96–103. doi:10.1111/j.1749-6632.2010.05627.x
46. Cheng G, Zielonka J, McAllister DM, et al. Mitochondria-targeted vitamin E analogs inhibit breast cancer cell energy metabolism and promote cell death. *BMC Cancer*. 2013;13:285. doi:10.1186/1471-2407-13-285
47. Battogtokh G, Choi YS, Kang DS, et al. Mitochondria-targeting drug conjugates for cytotoxic, anti-oxidizing and sensing purposes: current strategies and future perspectives. *Acta Pharm Sin B*. 2018;8(6):862–880. doi:10.1016/j.apsb.2018.05.006

48. Liang Y, Wang PY, Liu ZY, et al. Dual stimuli-responsive micelles for imaging-guided mitochondrion-targeted photothermal/photodynamic/chemo combination therapy-induced immunogenic cell death. *Int J Nanomed*. 2023;18:4381–4402. doi:10.2147/ijn.S410047
49. Cen J, Dai X, Zhao H, et al. Doxorubicin-loaded liposome with the function of "Killing two birds with one stone" against glioma. *ACS Appl Mater Interfaces*. 2023;15(40):46697–46709. doi:10.1021/acsami.3c10364
50. Cen J, Zhang R, Zhao T, et al. A water-soluble quercetin conjugate with triple targeting exerts neuron-protective effect on cerebral ischemia by mitophagy activation. *Adv Healthc Mater*. 2022;11(22):e2200817. doi:10.1002/adhm.202200817
51. Dai DF, Chen T, Szeto H, et al. Mitochondrial targeted antioxidant Peptide ameliorates hypertensive cardiomyopathy. *J Am Coll Cardiol*. 2011;58(1):73–82. doi:10.1016/j.jacc.2010.12.044
52. Gakh O, Cavadini P, Isaya G. Mitochondrial processing peptidases. *Biochim Biophys Acta*. 2002;1592(1):63–77. doi:10.1016/s0167-4889(02)00265-3
53. Jean SR, Ahmed M, Lei EK, Wisnovsky SP, Kelley SO. Peptide-mediated delivery of chemical probes and therapeutics to mitochondria. *Acc Chem Res*. 2016;49(9):1893–1902. doi:10.1021/acs.accounts.6b00277
54. Xun Z, Wipf P, McMurray CT. XJB-5-131 is a mild uncoupler of oxidative phosphorylation. *J Huntingtons Dis*. 2022;11(2):141–151. doi:10.3233/jhd-220539
55. Fink MP, Macias CA, Xiao J, et al. Hemigramicidin-TEMPO conjugates: novel mitochondria-targeted antioxidants. *Crit Care Med*. 2007;35(9 Suppl):S461–7. doi:10.1097/01.Ccm.0000279192.96303.E7
56. Hoye AT, Davoren JE, Wipf P, Fink MP, Kagan VE. Targeting mitochondria. *Acc Chem Res*. 2008;41(1):87–97. doi:10.1021/ar700135m
57. Kawamura E, Yamada Y, Harashima H. Mitochondrial targeting functional peptides as potential devices for the mitochondrial delivery of a DF-MITO-Porter. *Mitochondrion*. 2013;13(6):610–614. doi:10.1016/j.mito.2013.08.010
58. Huang Y, Ji W, Zhang J, et al. The involvement of the mitochondrial membrane in drug delivery. *Acta Biomater*. 2024;176:28–50. doi:10.1016/j.actbio.2024.01.027
59. Zou Y, Sun Y, Wang Y, et al. Cancer cell-mitochondria hybrid membrane coated Gboxin loaded nanomedicines for glioblastoma treatment. *Nat Commun*. 2023;14(1):4557. doi:10.1038/s41467-023-40280-3
60. Murphy MP. Targeting lipophilic cations to mitochondria. *Biochim Biophys Acta*. 2008;1777(7–8):1028–1031. doi:10.1016/j.bbabio.2008.03.029
61. Oyewole AO, Birch-Machin MA. Mitochondria-targeted antioxidants. *FASEB J*. 2015;29(12):4766–4771. doi:10.1096/fj.15-275404
62. Pawar A, Korake S, Pawar A, Kamble R. Delocalized lipophilic cation triphenyl phosphonium: promising molecule for mitochondria targeting. *Curr Drug Deliv*. 2023;20(9):1217–1223. doi:10.2174/1567201819666220525092527
63. Sanchez-Aranguren L, Al Tahan MA, Uppal M, Juvale P, Marwah MK. Mitochondrial-targeted liposome-based drug delivery - therapeutic potential and challenges. *J Drug Target*. 2025;33(5):575–586. doi:10.1080/1061186x.2024.2437440
64. Liao J, He W, Li L, et al. Mitochondria in brain diseases: bridging structural-mechanistic insights into precision-targeted therapies. *Cell Biomaterials*. 2025;1(2):100016. doi:10.1016/j.celbio.2025.100016
65. Jiang Q, Yin J, Chen J, et al. Mitochondria-targeted antioxidants: a step towards disease treatment. *Oxid Med Cell Longev*. 2020;2020:8837893. doi:10.1155/2020/8837893
66. Murphy MP, Smith RA. Targeting antioxidants to mitochondria by conjugation to lipophilic cations. *Annu Rev Pharmacol Toxicol*. 2007;47:629–656. doi:10.1146/annurev.pharmtox.47.120505.105110
67. Fairley LH, Das S, Dharwal V, et al. Mitochondria-targeted antioxidants as a therapeutic strategy for chronic obstructive pulmonary disease. *Antioxidants*. 2023;12(4). doi:10.3390/antiox12040973
68. Stelmashook EV, Isaev NK, Genrikhs EE, Novikova SV. Mitochondria-targeted antioxidants as potential therapy for the treatment of traumatic brain injury. *Antioxidants*. 2019;8(5). doi:10.3390/antiox8050124
69. Matondo A, Kim SS. Targeted-mitochondria antioxidants therapeutic implications in inflammatory bowel disease. *J Drug Target*. 2018;26(1):1–8. doi:10.1080/1061186x.2017.1339196
70. Kim HK, Han J. Mitochondria-targeted antioxidants for the treatment of cardiovascular disorders. *Adv Exp Med Biol*. 2017;982:621–646. doi:10.1007/978-3-319-55330-6_32
71. Kezic A, Spasojevic I, Lezaic V, Bajcetic M. Mitochondria-targeted antioxidants: future perspectives in kidney ischemia reperfusion injury. *Oxid Med Cell Longev*. 2016;2016:2950503. doi:10.1155/2016/2950503
72. Jin H, Kanthasamy A, Ghosh A, Anantharam V, Kalyanaraman B, Kanthasamy AG. Mitochondria-targeted antioxidants for treatment of Parkinson's disease: preclinical and clinical outcomes. *Biochim Biophys Acta*. 2014;1842(8):1282–1294. doi:10.1016/j.bbadis.2013.09.007
73. Manczak M, Mao P, Calkins MJ, et al. Mitochondria-targeted antioxidants protect against amyloid-beta toxicity in Alzheimer's disease neurons. *J Alzheimers Dis*. 2010;20(Suppl 2):S609–31. doi:10.3233/jad-2010-100564
74. Zeng S, Liu X, Kafuti YS, et al. Fluorescent dyes based on rhodamine derivatives for bioimaging and therapeutics: recent progress, challenges, and prospects. *Chem Soc Rev*. 2023;52(16):5607–5651. doi:10.1039/d2cs00799a
75. Emaus RK, Grunwald R, Lemasters JJ. Rhodamine 123 as a probe of transmembrane potential in isolated rat-liver mitochondria: spectral and metabolic properties. *Biochim Biophys Acta*. 1986;850(3):436–448. doi:10.1016/0005-2728(86)90112-x
76. Rahman KMM, Bist G, Kumbham S, Foster BA, Woo S, You Y. Mitochondrial targeting improves the selectivity of singlet-oxygen cleavable prodrugs in NMIBC treatment. *Photochem Photobiol*. 2024;100(6):1622–1635. doi:10.1111/php.13928
77. Desai S, Grefte S, van de Westerlo E, et al. Performance of TMRM and Mitotrackers in mitochondrial morphofunctional analysis of primary human skin fibroblasts. *Biochim Biophys Acta Bioenergy*. 2024;1865(2):149027. doi:10.1016/j.bbabio.2023.149027
78. Sato H, Nishiyama M, Morita N, et al. Mitochondrial connexin43 and mitochondrial K(ATP) channels modulate triggered arrhythmias in mouse ventricular muscle. *Pflugers Arch*. 2023;475(4):477–488. doi:10.1007/s00424-023-02789-w
79. Yang RZ, Wang DD, Li SM, Liu PP, Kang JS. Measurement of mitochondrial membrane potential in vivo using a genetically encoded voltage indicator. *J Vis Exp*. 2025;(216). doi:10.3791/67911
80. Zhang L, Jiang FL, Guo QL, Liu Y, Jiang P. pH-sensitive bioprobe for multichannel mitochondrial imaging and photodynamic therapy. *Anal Chem*. 2022;94(9):4126–4133. doi:10.1021/acs.analchem.2c00306
81. Wang J, He H, Xiang C, et al. Uncoupling effect of F16 is responsible for its mitochondrial toxicity and anticancer activity. *Toxicol Sci*. 2018;161(2):431–442. doi:10.1093/toxsci/kfx218

82. Xu J, He H, Zhou LJ, et al. Pyridinium and indole orientation determines the mitochondrial uncoupling and anti-cancer efficiency of F16. *Eur J Med Chem*. 2018;154:305–313. doi:10.1016/j.ejmech.2018.05.036
83. Miao H, Cui W, Zhang T, et al. Mitochondrial targeting derivatives of honokiol enhanced selective antitumor activity in NCI-H446 cells and decreased in vivo toxicity in Caenorhabditis elegans. *Eur J Med Chem*. 2024;264:115996. doi:10.1016/j.ejmech.2023.115996
84. Pawar A, Korake S, Gajbhiye KR. Dequalinium-derived nanoconstructs: a promising vehicle for mitochondrial targeting. *Curr Drug Deliv*. 2021;18(8):1056–1063. doi:10.2174/1567201818999210120201252
85. Bae Y, Jung MK, Lee S, et al. Dequalinium-based functional nanosomes show increased mitochondria targeting and anticancer effect. *Eur J Pharm Biopharm*. 2018;124:104–115. doi:10.1016/j.ejpb.2017.12.013
86. Thuy LT, Lee S, Dongquoc V, Choi JS. Nanoemulsion composed of α-tocopherol succinate and dequalinium shows mitochondria-targeting and anticancer effects. *Antioxidants*. 2023;12(2). doi:10.3390/antiox12020437
87. Weissig V, Lozoya M, Yu N, GGM D. DQAsomes as the prototype of mitochondria-targeted pharmaceutical nanocarriers: an update. *Methods Mol Biol*. 2021;2275:13–25. doi:10.1007/978-1-0716-1262-0_2
88. Wang M, Zhang M, Hu X, et al. Lipid-functionalized gold nanorods with plug-to-direct mitochondria targeting ligand for synergetic photothermal-chemotherapy of tumor therapy. *Eur J Pharm Biopharm*. 2023;185:71–81. doi:10.1016/j.ejpb.2023.02.010
89. Keethedeth N, Anantha Shenoi R. Mitochondria-targeted nanotherapeutics: a new frontier in neurodegenerative disease treatment. *Mitochondrion*. 2025;81:102000. doi:10.1016/j.mito.2024.102000
90. Zhao K, Zhao GM, Wu D, et al. Cell-permeable peptide antioxidants targeted to inner mitochondrial membrane inhibit mitochondrial swelling, oxidative cell death, and reperfusion injury. *J Biol Chem*. 2004;279(33):34682–34690. doi:10.1074/jbc.M402999200
91. Szeto HH. Mitochondria-targeted cytoprotective peptides for ischemia-reperfusion injury. *Antioxid Redox Signal*. 2008;10(3):601–619. doi:10.1089/ars.2007.1892
92. Wu J, Zhang M, Hao S, et al. Mitochondria-targeted peptide reverses mitochondrial dysfunction and cognitive deficits in sepsis-associated encephalopathy. *Mol Neurobiol*. 2015;52(1):783–791. doi:10.1007/s12035-014-8918-z
93. Szeto HH, Liu S. Cardiolipin-targeted peptides rejuvenate mitochondrial function, remodel mitochondria, and promote tissue regeneration during aging. *Arch Biochem Biophys*. 2018;660:137–148. doi:10.1016/j.abb.2018.10.013
94. Zhang X, Sun Y, Yang R, et al. An injectable mitochondria-targeted nanodrug loaded-hydrogel for restoring mitochondrial function and hierarchically attenuating oxidative stress to reduce myocardial ischemia-reperfusion injury. *Biomaterials*. 2022;287:121656. doi:10.1016/j.biomaterials.2022.121656
95. Cerrato CP, Pirisinu M, Vlachos EN, Ü L. Novel cell-penetrating peptide targeting mitochondria. *FASEB j*. 2015;29(11):4589–4599. doi:10.1096/fj.14-269225
96. Mitchell W, Tamucci JD, Ng EL, et al. Structure-activity relationships of mitochondria-targeted tetrapeptide pharmacological compounds. *Elife*. 2022;11. doi:10.7554/eLife.75531
97. Zheng Z, Lei C, Liu H, et al. A ROS-responsive liposomal composite hydrogel integrating improved mitochondrial function and pro-angiogenesis for efficient treatment of myocardial infarction. *Adv Healthc Mater*. 2022;11(19):e2200990. doi:10.1002/adhm.202200990
98. Qian W, Liu D, Liu J, et al. The mitochondria-targeted micelle inhibits Alzheimer's disease progression by alleviating neuronal mitochondrial dysfunction and neuroinflammation. *Small*. 2025;21(6):e2408581. doi:10.1002/smll.202408581
99. Wang C, Li H, Li F, et al. The mitochondrial protectant SS31 optimized decellularized Wharton's jelly scaffold improves allogeneic chondrocyte implantation-mediated articular cartilage repair. *J Orthop Translat*. 2025;52:126–137. doi:10.1016/j.jot.2025.03.023
100. Qian J, Guo Y, Xu Y, Wang X, Chen J, Wu X. Combination of micelles and liposomes as a promising drug delivery system: a review. *Drug Deliv Transl Res*. 2023;13(11):2767–2789. doi:10.1007/s13346-023-01368-x
101. Pei J, Palanisamy CP, Natarajan PM, et al. Curcumin-loaded polymeric nanomaterials as a novel therapeutic strategy for Alzheimer's disease: a comprehensive review. *Ageing Res Rev*. 2024;99:102393. doi:10.1016/j.arr.2024.102393
102. Xiong L, Hu H, Zhu F, et al. New insight for SS-31 in treating diabetic cardiomyopathy: activation of mitoGPX4 and alleviation of mitochondria-dependent ferroptosis. *Int J Mol Med*. 2024;54(6). doi:10.3892/ijmm.2024.5436
103. Zhu Y, Luo M, Bai X, et al. SS-31, a mitochondria-targeting peptide, ameliorates kidney disease. *Oxid Med Cell Longev*. 2022;2022:1295509. doi:10.1155/2022/1295509
104. Du X, Zeng Q, Luo Y, et al. Application research of novel peptide mitochondrial-targeted antioxidant SS-31 in mitigating mitochondrial dysfunction. *Mitochondrion*. 2024;75:101846. doi:10.1016/j.mito.2024.101846
105. Gong W, Liu Z, Wang Y, et al. Reprogramming of Treg cell-derived small extracellular vesicles effectively prevents intestinal inflammation from PANoptosis by blocking mitochondrial oxidative stress. *Trends Biotechnol*. 2024. doi:10.1016/j.tibtech.2024.11.017
106. Zhao T, He F, Zhao K, et al. A triple-targeted Rutin-based self-assembled delivery vector for treating ischemic stroke by vascular normalization and anti-inflammation via ACE2/Ang1-7 signaling. *ACS Cent Sci*. 2023;9(6):1180–1199. doi:10.1021/acscentsci.3c00377
107. Zhang Y, Zhang H, Zhao F, et al. Mitochondrial-targeted and ROS-responsive nanocarrier via nose-to-brain pathway for ischemic stroke treatment. *Acta Pharm Sin B*. 2023;13(12):5107–5120. doi:10.1016/j.apsb.2023.06.011
108. Xun Z, Rivera-Sánchez S, Ayala-Peña S, et al. Targeting of XJB-5-131 to mitochondria suppresses oxidative DNA damage and motor decline in a mouse model of Huntington's disease. *Cell Rep*. 2012;2(5):1137–1142. doi:10.1016/j.celrep.2012.10.001
109. Fink MP, Macias CA, Xiao J, et al. Hemigramicidin-TEMPO conjugates: novel mitochondria-targeted anti-oxidants. *Biochem Pharmacol*. 2007;74(6):801–809. doi:10.1016/j.bcp.2007.05.019
110. Wipf P, Polyzos AA, McMurray CT. A Double-Pronged Sword: XJB-5-131 is a suppressor of somatic instability and toxicity in Huntington's disease. *J Huntingtons Dis*. 2022;11(1):3–15. doi:10.3233/jhd-210510
111. Sun W, Lv Z, Li W, et al. XJB-5-131 protects chondrocytes from ferroptosis to alleviate osteoarthritis progression via restoring Pebp1 expression. *J Orthop Translat*. 2024;44:114–124. doi:10.1016/j.jot.2023.12.005
112. Singh D. A sojourn on mitochondria targeted drug delivery systems for cancer: strategies, clinical and future prospects. *Mitochondrion*. 2024;74:101826. doi:10.1016/j.mito.2023.101826
113. Zhou M, Li L, Li L, et al. Overcoming chemotherapy resistance via simultaneous drug-efflux circumvention and mitochondrial targeting. *Acta Pharm Sin B*. 2019;9(3):615–625. doi:10.1016/j.apsb.2018.11.005

114. Wu J, Li J, Wang H, Liu C-B. Mitochondrial-targeted penetrating peptide delivery for cancer therapy. *Expert Opin Drug Deliv*. 2018;15(10):951–964. doi:10.1080/17425247.2018.1517750
115. Folgar-Cameán Y, Torralba-Maldonado D, Fulias-Guzmán P, et al. A non-hydrolysable peptidomimetic for mitochondrial targeting. *J Mater Chem B*. 2025;13(10):3365–3373. doi:10.1039/d4tb01626b
116. Yoshinaga N, Numata K. Poly(A) tail length of messenger RNA regulates translational efficiency of the mitochondria-targeting delivery system. *ACS Biomater Sci Eng*. 2024;10(10):6344–6351. doi:10.1021/acsbiomaterials.4c01169
117. Sack T, Dhavarasa P, Szames D, O'Brien S, Angers S, Kelley SO. CRISPR SCREENING in Tandem with targeted mtDNA damage reveals WRNIP1 essentiality. *ACS Chem Biol*. 2023;18(12):2599–2609. doi:10.1021/acschembio.3c00620
118. Boob AG, Tan SI, Zaidi A, et al. Design of diverse, functional mitochondrial targeting sequences across eukaryotic organisms using variational autoencoder. *Nat Commun*. 2025;16(1):4151. doi:10.1038/s41467-025-59499-3
119. Pegoraro C, Karpova E, Qutbuddin Y, et al. Polyproline-Polyornithine Diblock copolymers with inherent mitochondria tropism. *Adv Mater*. 2025;37(8):e2411595. doi:10.1002/adma.202411595
120. Yamada Y, Harashima H. MITO-Porter for mitochondrial delivery and mitochondrial functional analysis. *Handb Exp Pharmacol*. 2017;240:457–472. doi:10.1007/164_2016_4
121. Yamada Y, Harashima H. Delivery of bioactive molecules to the mitochondrial genome using a membrane-fusing, liposome-based carrier, DF-MITO-Porter. *Biomaterials*. 2012;33(5):1589–1595. doi:10.1016/j.biomaterials.2011.10.082
122. Norota K, Ishizuka S, Hirose M, et al. Lipid nanoparticle delivery of the CRISPR/Cas9 system directly into the mitochondria of cells carrying m.7778G>T mutation in MtDNA (mt-Atp8). *Sci Rep*. 2025;15(1):18717. doi:10.1038/s41598-025-03671-8
123. Hibino M, Filosi T, Carrion LL, et al. An effective approach to modulate mitochondrial function in murine primary macrophages by a mitochondria-targeted nanocapsule, MITO-Porter. *Biomed Pharmacother*. 2025;186:118019. doi:10.1016/j.biopha.2025.118019
124. Kawamura E, Maruyama M, Abe J, et al. Validation of gene therapy for mutant mitochondria by delivering mitochondrial RNA using a MITO-Porter. *Mol Ther Nucleic Acids*. 2020;20:687–698. doi:10.1016/j.omtn.2020.04.004
125. Sato Y, Nakamura T, Yamada Y, Harashima H. The nanomedicine rush: new strategies for unmet medical needs based on innovative nano DDS. *J Control Release*. 2021;330:305–316. doi:10.1016/j.jconrel.2020.12.032
126. Naganawa R, Zhao H, Takano Y, et al. Investigation of the nanoparticulation method and cell-killing effect following the mitochondrial delivery of hydrophobic porphyrin-based photosensitizers. *Int J Mol Sci*. 2024;25(8). doi:10.3390/ijms25084294
127. Sato Y, Nakamura T, Yamada Y, Harashima H. The impact of, and expectations for, lipid nanoparticle technology: from cellular targeting to organelle targeting. *J Control Release*. 2024;370:516–527. doi:10.1016/j.jconrel.2024.05.006
128. Liao J, Gong L, Xu Q, et al. Revolutionizing neurocare: biomimetic nanodelivery via cell membranes. *Adv Mater*. 2024;36(26):e2402445. doi:10.1002/adma.202402445
129. Mengyuan H, Aixue L, Yongwei G, et al. Biomimetic nanocarriers in cancer therapy: based on intercellular and cell-tumor microenvironment communication. *J Nanobiotechnol*. 2024;22(1):604. doi:10.1186/s12951-024-02835-4
130. Zhou Y, Wang X, Tian X, et al. Stealth missiles with precision guidance: a novel multifunctional nano-drug delivery system based on biomimetic cell membrane coating technology. *Mater Today Bio*. 2025;33:101922. doi:10.1016/j.mtbio.2025.101922
131. Qureshi SA, Rafiya K, Awasthi S, et al. Biomembrane camouflaged nanoparticles: a paradigm shifts in targeted drug delivery system. *Colloids Surf B Biointerfaces*. 2024;238:113893. doi:10.1016/j.colsurfb.2024.113893
132. Zhu A, Jiang Y, Pan L, et al. Cell inspired delivery system equipped with natural membrane structures in applications for rescuing ischemic stroke. *J Control Release*. 2025;377:54–80. doi:10.1016/j.jconrel.2024.11.013
133. Wieckowski MR, Giorgi C, Lebiedzinska M, Duszynski J, Pinton P. Isolation of mitochondria-associated membranes and mitochondria from animal tissues and cells. *Nat Protoc*. 2009;4(11):1582–1590. doi:10.1038/nprot.2009.151
134. Pan Y, He Y, Zhao X, et al. Engineered red blood cell membrane-coating salidroside/indocyanine green nanovesicles for high-efficiency hypoxic targeting phototherapy of triple-negative breast cancer. *Adv Healthc Mater*. 2022;11(17):e2200962. doi:10.1002/adhm.202200962
135. Li C, Zhao Z, Luo Y, et al. Macrophage-disguised manganese dioxide nanoparticles for neuroprotection by reducing oxidative stress and modulating inflammatory microenvironment in acute ischemic stroke. *Adv Sci*. 2021;8(20):e2101526. doi:10.1002/advs.202101526
136. Wu HH, Zhou Y, Tabata Y, Gao JQ. Mesenchymal stem cell-based drug delivery strategy: from cells to biomimetic. *J Control Release*. 2019;294:102–113. doi:10.1016/j.jconrel.2018.12.019
137. Duan R, Sun K, Fang F, et al. An ischemia-homing bioengineered nano-scavenger for specifically alleviating multiple pathogeneses in ischemic stroke. *J Nanobiotechnol*. 2022;20(1):397. doi:10.1186/s12951-022-01602-7
138. Chen H, Pu W, Hu X, et al. Rational engineering of a mitochondrial-mimetic therapy for targeted treatment of dilated cardiomyopathy by precisely regulating mitochondrial homeostasis. *Adv Funct Mater*. 2023;33(49):2301918.2301918. doi:10.1002/adfm.202301918
139. Liu H, Tang L, Yin Y, et al. Photoresponsive multirole nanoweapon camouflaged by hybrid cell membrane vesicles for efficient antibacterial therapy of Pseudomonas aeruginosa-infected pneumonia and wound. *Adv Sci*. 2024;11(35):e2403101. doi:10.1002/advs.202403101
140. Cao Y, Tang L, Fu C, et al. Black phosphorus quantum dot loaded bioinspired nanoplatform synergized with aPD-L1 for multimode cancer immunotherapy. *Nano Lett*. 2024;24(22):6767–6777. doi:10.1021/acs.nanolett.4c01511
141. Deng Y, Liu Z, Lu M. Extracellular vesicles deviced from hypoxia-3D-GMSCs rescue the mitochondrial dysfunction of aging-GMSCs. *Biochem Biophys Res Commun*. 2024;717:150021. doi:10.1016/j.bbrc.2024.150021
142. Ma Z, Han H, Zhao Y. Mitochondrial dysfunction-targeted nanosystems for precise tumor therapeutics. *Biomaterials*. 2023;293121947. doi:10.1016/j.biomaterials.2022.121947
143. Forini F, Canale P, Nicolini G, Iervasi G. Mitochondria-targeted drug delivery in cardiovascular disease: a long road to nano-cardio medicine. *Pharmaceutics*. 2020;12(11):1122. doi:10.3390/pharmaceutics12111122
144. Oladimeji O, Akinyelu J, Singh M. Nanomedicines for subcellular targeting: the mitochondrial perspective. *Curr Med Chem*. 2020;27(33):5480–5509. doi:10.2174/0929867326666191125092111
145. Tabish TA, Hamblin MR. Mitochondria-targeted nanoparticles (mitoNANO): an emerging therapeutic shortcut for cancer. *Biomaterials and Biosystems*. 2021;3:100023. doi:10.1016/j.bbiosy.2021.100023
146. Qin J, Gong N, Liao Z, et al. Recent progress in mitochondria-targeting-based nanotechnology for cancer treatment. *Nanoscale*. 2021;13(15):7108–7118. doi:10.1039/d1nr01068a

147. Wang H, Tang C, Xiang Y, et al. Tea polyphenol-derived nanomedicine for targeted photothermal thrombolysis and inflammation suppression. *J Nanobiotechnol*. 2024;22(1):146. doi:10.1186/s12951-024-02446-z
148. Long X, Liu M, Nan Y, et al. Revitalizing ancient mitochondria with nano-strategies: mitochondria-remedying nanodrugs concentrate on disease control. *Adv Mater*. 2024;36(18). doi:10.1002/adma.202308239
149. Gao C, Wang Y, Sun J, et al. Neuronal mitochondria-targeted delivery of curcumin by biomimetic engineered nanosystems in Alzheimer's disease mice. *Acta Biomater*. 2020;108:285–299. doi:10.1016/j.actbio.2020.03.029
150. Yang P, Sheng D, Guo Q, et al. Neuronal mitochondria-targeted micelles relieving oxidative stress for delayed progression of Alzheimer's disease. *Biomaterials*. 2020:238119844. doi:10.1016/j.biomaterials.2020.119844
151. Han Y, Chu X, Cui L, et al. Neuronal mitochondria-targeted therapy for Alzheimer's disease by systemic delivery of resveratrol using dual-modified novel biomimetic nanosystems. *Drug Delivery*. 2020;27(1):502–518. doi:10.1080/10717544.2020.1745328
152. Han Y, Gao C, Wang H, et al. Macrophage membrane-coated nanocarriers co-modified by RVG29 and TPP improve brain neuronal mitochondria-targeting and therapeutic efficacy in Alzheimer's disease mice. *Bioact Mater*. 2021;6(2):529–542. doi:10.1016/j.bioactmat.2020.08.017
153. Liu Y, Zhao D, Yang F, et al. In situ self-assembled phytopolyphenol-coordinated intelligent nanotherapeutics for multipronged management of ferroptosis-driven Alzheimer's disease. *ACS Nano*. 2024;18(11):7890–7906. doi:10.1021/acsnano.3c09286
154. Li Y, Zhou Z, Chen S, et al. Mitochondria-targeting fluorescent sensor with high photostability and permeability for visualizing viscosity in mitochondrial malfunction, inflammation, and AD models. *Anal Chim Acta*. 2023;1250:340967. doi:10.1016/j.aca.2023.340967
155. Ren C, Li D, Zhou Q, Hu X. Mitochondria-targeted TPP-MoS2 with dual enzyme activity provides efficient neuroprotection through M1/M2 microglial polarization in an Alzheimer's disease model. *Biomaterials*. 2020;232119752. doi:10.1016/j.biomaterials.2019.119752
156. Kwon HJ, Cha M-Y, Kim D, et al. Mitochondria-targeting ceria nanoparticles as antioxidants for Alzheimer's disease. *ACS Nano*. 2016;10(2):2860–2870. doi:10.1021/acsnano.5b08045
157. Zhang S, Li M, Li Y, et al. Mitochondria-targeted nanovesicles for ursodeoxycholic acid delivery to combat neurodegeneration by ameliorating mitochondrial dysfunction. *J Nanobiotechnol*. 2025;23(1):202.202. doi:10.1186/s12951-025-03258-5
158. Xia X, Li H, Xu X, Zhao G, Du M. Facilitating pro-survival mitophagy for alleviating Parkinson's disease via sequence-targeted lycopene nanodots. *ACS Nano*. 2023;17(18):17979–17995. doi:10.1021/acsnano.3c04308
159. Zheng Q, Liu H, Zhang H, et al. Ameliorating mitochondrial dysfunction of neurons by biomimetic targeting nanoparticles mediated mitochondrial biogenesis to boost the therapy of Parkinson's disease. *Adv Sci*. 2023;10(22):2300758. doi:10.1002/advs.202300758
160. Li B, Bai Y, Yion C, et al. Single-atom nanocatalytic therapy for suppression of neuroinflammation by inducing autophagy of abnormal mitochondria. *ACS Nano*. 2023;17(8):7511–7529. doi:10.1021/acsnano.2c12614
161. Lei L, Yuan J, Dai Z, et al. Targeting the labile iron pool with engineered DFO nanosheets to inhibit ferroptosis for Parkinson's disease therapy. *Adv Mater*. 2024;36(41):2409329. doi:10.1002/adma.202409329
162. Liu Y, Liu Y, Shi P, et al. Single-atom nanozyme liposome-integrated microneedles for in situ drug delivery and anti-inflammatory therapy in Parkinson's disease. *J Nanobiotechnol*. 2024;22(1):643. doi:10.1186/s12951-024-02924-4
163. Kang JH, Ko YT. Dual-selective photodynamic therapy with a mitochondria-targeted photosensitizer and fiber optic cannula for malignant brain tumors. *Biomater Sci*. 2019;7(7):2812–2825. doi:10.1039/c9bm00403c
164. Cao TGN, Kang JH, Kang SJ, et al. Brain endothelial cell-derived extracellular vesicles with a mitochondria-targeting photosensitizer effectively treat glioblastoma by hijacking the blood-brain barrier. *Acta Pharmaceutica Sinica B*. 2023;13(9):3834–3848. doi:10.1016/j.apsb.2023.03.023
165. Zhao Y, Peng Y, Yang Z, et al. pH-redox responsive cascade-targeted liposomes to intelligently deliver doxorubicin prodrugs and lonidamine for glioma. *Eur J Med Chem*. 2022:235114281. doi:10.1016/j.ejmech.2022.114281
166. Jin L, Xu Y, Chen F, et al. Mitochondria-targeted and pH-triggered charge-convertible polymeric micelles for anticancer therapy. *Mater Des*. 2022:224111290. doi:10.1016/j.matdes.2022.111290
167. Xiang Y, Wang B, Yang W, et al. Mitocytosis mediated by an enzyme-activable mitochondrion-disturbing polymer-drug conjugate enhances active penetration in glioblastoma therapy. *Adv Mater*. 2024;36(18). doi:10.1002/adma.202311500
168. Tang M, Lin K, Ramachandran M, et al. A mitochondria-targeting lipid-small molecule hybrid nanoparticle for imaging and therapy in an orthotopic glioma model. *Acta Pharmaceutica Sinica B*. 2022;12(6):2672–2682. doi:10.1016/j.apsb.2022.04.005
169. Gao X, Tang X, Tu Z, et al. Tertiary amine modification enables triterpene nanoparticles to target the mitochondria and treat glioblastoma via pyroptosis induction. *Biomaterials*. 2025:317123035. doi:10.1016/j.biomaterials.2024.123035
170. Ye Y, Ren K, Dong Y, et al. Mitochondria-targeting pyroptosis amplifier of lonidamine-modified black phosphorus nanosheets for glioblastoma treatments. *ACS Appl Mater Interfaces*. 2023;15(22):26285–26297. doi:10.1021/acsami.3c01559
171. Chen Y, Tian H, Zhang X, et al. Copper-coordination driven brain-targeting nanoassembly for efficient glioblastoma multiforme immunotherapy by cuproptosis-mediated tumor immune microenvironment reprogramming. *J Nanobiotechnol*. 2024;22(1):801. doi:10.1186/s12951-024-03059-2
172. Kaundal B, Karmakar S, Choudhury SR. Mitochondria-targeting nano therapy altering IDH2-mediated EZH2/EZH1 interaction as precise epigenetic regulation in glioblastoma. *Biomater Sci*. 2022;10(18):5301–5317. doi:10.1039/d1bm02006d
173. Deng K, Zhang L, Gao W, et al. A functional carbon dots induce ferroptosis by suppressing PLPP4 activity to inhibit glioblastoma growth. *Chem Eng J*. 2023:475146473. doi:10.1016/j.cej.2023.146473
174. Wang Z, Pan J, Yuan R, Chen M, Guo X, Zhou S. Shell-sheddable polymeric micelles alleviate oxidative stress and inflammation for enhanced ischemic stroke therapy. *Nano Lett*. 2023;23(14):6544–6552. doi:10.1021/acs.nanolett.3c01567
175. Liao J, Li Y, Fan L, et al. Bioactive ceria nanoenzymes target mitochondria in reperfusion injury to treat ischemic stroke. *ACS Nano*. 2024;18(7):5510–5529. doi:10.1021/acsnano.3c10982
176. Liao J, He W, Zhang S, et al. Magnetic field driven ceria nanosystems for mitochondria targeted therapy of ischemic stroke. *Adv Funct Mater*. 2025. doi:10.1002/adfm.202423291
177. Sharma A, Liaw K, Sharma R, Zhang Z, Kannan S, Kannan RM. Targeting mitochondrial dysfunction and oxidative stress in activated microglia using Dendrimer-based therapeutics. *Theranostics*. 2018;8(20):5529–5547. doi:10.7150/thno.29039
178. Sun J, Liu J, Gao C, et al. Targeted delivery of PARP inhibitors to neuronal mitochondria via biomimetic engineered nanosystems in a mouse model of traumatic brain injury. *Acta Biomater*. 2022;140:573–585. doi:10.1016/j.actbio.2021.12.023

179. Pan X, Zuo Z, Wang Z, et al. Ligand engineering of luminescent AuAg nanoclusters for targeted mitochondrial and brain imaging. *Mater Chem Front*. 2023;7(6):1146–1152. doi:10.1039/D2QM01125E
180. Terstappen GC, Meyer AH, Bell RD, Zhang W. Strategies for delivering therapeutics across the blood-brain barrier. *Nat Rev Drug Discov*. 2021;20(5):362–383. doi:10.1038/s41573-021-00139-y
181. Han L, Jiang C. Evolution of blood-brain barrier in brain diseases and related systemic nanoscale brain-targeting drug delivery strategies. *Acta Pharm Sin B*. 2021;11(8):2306–2325. doi:10.1016/j.apsb.2020.11.023
182. Xu J, Du W, Zhao Y, et al. Mitochondria targeting drugs for neurodegenerative diseases-design, mechanism and application. *Acta Pharmaceutica Sinica B*. 2022;12(6):2778–2789. doi:10.1016/j.apsb.2022.03.001
183. Yue Z, Han Y, Daohe W, et al. Mitochondria-targeted nanoparticles in treatment of neurodegenerative diseases. *Exploration*. 2021;1 (3):20210115. doi:10.1002/EXP.20210115
184. Plascencia-Villa G, Perry G. Exploring molecular targets for mitochondrial therapies in neurodegenerative diseases. *Int J Mol Sci*. 2023;24 (15):12486. doi:10.3390/ijms241512486
185. Tapia-Arellano A, Cabrera P, Cortes-Adasme E, Riveros A, Hassan N, Kogan MJ. Tau- and α-synuclein-targeted gold nanoparticles: applications, opportunities, and future outlooks in the diagnosis and therapy of neurodegenerative diseases. *J Nanobiotechnol*. 2024;22 (1):248. doi:10.1186/s12951-024-02526-0
186. Liu Y, Tan Y, Cheng G, et al. Customized intranasal hydrogel delivering methylene blue ameliorates cognitive dysfunction against Alzheimer's disease. *Adv Mater*. 2024;36(19). doi:10.1002/adma.202307081
187. Li W, Peng X, Mei X, Dong M, Li Y, Dong H. Multifunctional DNA tetrahedron for Alzheimer's disease mitochondria-targeted therapy by microRNA regulation. *ACS Appl Mater Interfaces*. 2023;15(19):22977–22984. doi:10.1021/acsami.3c03181
188. Szeto HH. First-in-class cardiolipin-protective compound as a therapeutic agent to restore mitochondrial bioenergetics. Review. *Br J Pharmacol*. 2014;171(8):2029–2050. doi:10.1111/bph.12461
189. Reddy PH, Manczak M, Kandimalla R. Mitochondria-targeted small molecule SS31: a potential candidate for the treatment of Alzheimer's disease. *Human Mol Genetics*. 2017;26(8):1483–1496. doi:10.1093/hmg/ddx052
190. Reddy PH, Manczak M, Yin X, Reddy AP. Synergistic protective effects of mitochondrial division inhibitor 1 and mitochondria-targeted small peptide SS31 in Alzheimer's disease. *J Alzheimers Dis*. 2018;62(4):1549–1565. doi:10.3233/jad-170988
191. Ding X-W, Robinson M, Li R, Aldhowayan H, Geetha T, Babu JR. Mitochondrial dysfunction and beneficial effects of mitochondria-targeted small peptide SS-31 in diabetes mellitus and Alzheimer's disease. *Rev Pharmacol Res*. 2021;171105783. doi:10.1016/j.phrs.2021.105783
192. Puspita L, Chung SY, J-w S. Oxidative stress and cellular pathologies in Parkinson's disease. *Rev Molecular Brain*. 2017;1053. doi:10.1186/s13041-017-0340-9
193. Zheng Q, Liu H, Gao Y, Cao G, Wang Y, Li Z. Ameliorating mitochondrial dysfunction for the therapy of Parkinson's disease. *Small*. 2024;20 (29). doi:10.1002/smll.202311571
194. Wang H-X, Zuo Z-Q, Du J-Z, et al. Surface charge critically affects tumor penetration and therapeutic efficacy of cancer nanomedicines. *Nano Today*. 2016;11(2):133–144. doi:10.1016/j.nantod.2016.04.008
195. Li Y, Yang HY, Thambi T, Park J-H, Lee DS. Charge-convertible polymers for improved tumor targeting and enhanced therapy. *Biomaterials*. 2019;217119299. doi:10.1016/j.biomaterials.2019.119299
196. Pandey A, Singh K, Subramanian S, Korde A, Singh R, Sawant K. Heterogeneous surface architectured pH responsive metal-drug nano-conjugates for mitochondria targeted therapy of glioblastomas: a multimodal intranasal approach. *Chem Eng J*. 2020;394124419. doi:10.1016/j.cej.2020.124419
197. You Q, Liang F, Wu G, et al. The landscape of biomimetic nanovesicles in brain diseases. *Adv Mater*. 2024;36(7). doi:10.1002/adma.202306583
198. Wu H, Zhang T, Li N, Gao J. Cell membrane-based biomimetic vehicles for effective central nervous system target delivery: insights and challenges. *J Control Release*. 2023;360:169–184. doi:10.1016/j.jconrel.2023.06.023
199. Zou Y, Wang Y, Xu S, et al. Brain co-delivery of temozolomide and cisplatin for combinatorial glioblastoma chemotherapy. *Adv Mater*. 2022;34 (33):2203958. doi:10.1002/adma.202203958
200. Shichita T, Ooboshi H, Yoshimura A. Neuroimmune mechanisms and therapies mediating post-ischaemic brain injury and repair. Review. *Nat Rev Neurosci*. 2023;24(5):299–312. doi:10.1038/s41583-023-00690-0
201. Huang Q, Liao J, Li J, et al. Curcumin-loaded ceria nanoenzymes for dual-action suppression of inflammation and alleviation of oxidative damage in the treatment of acute lung injury. *Chin Chem Lett*. 2025;36(4):109914. doi:10.1016/j.cclet.2024.109914
202. Cheng F, Wang S, Zheng H, et al. Ceria nanoenzyme-based hydrogel with antiglycative and antioxidative performance for infected diabetic wound healing. *Small Methods*. 2022;6(11):2200949. doi:10.1002/smtd.202200949
203. Lamade AM, Kenny EM, Anthonymuthu TS, et al. Aiming for the target: mitochondrial drug delivery in traumatic brain injury. *Neuropharmacology*. 2019;145:209–219. doi:10.1016/j.neuropharm.2018.07.014
204. Alexander JF, Mahalingam R, Seua AV, et al. Targeting the meningeal compartment to resolve chemobrain and neuropathy via nasal delivery of functionalized mitochondria. *Adv Healthcare Mater*. 2022;11(8):2102153. doi:10.1002/adhm.202102153
205. Tabassum S, Wu S, Lee C-H, et al. Mitochondrial-targeted therapies in traumatic brain injury: from bench to bedside. Review. *Neurotherapeutics*. 2025;22(1):e00515. doi:10.1016/j.neurot.2024.e00515
206. Gil S, Correia CR, Mano JF. Magnetically labeled cells with surface-modified fe3 o4 spherical and rod-shaped magnetic nanoparticles for tissue engineering applications. *Adv Healthc Mater*. 2015;4(6):883–891. doi:10.1002/adhm.201400611
207. Son J, Kalafatovic D, Kumar M, et al. Customizing morphology, size, and response kinetics of matrix metalloproteinase-responsive nanostructures by systematic peptide design. *ACS Nano*. 2019;13(2):1555–1562. doi:10.1021/acsnano.8b07401
208. Alle M, Sharma G, Lee SH, Kim JC. Next-generation engineered nanogold for multimodal cancer therapy and imaging: a clinical perspectives. *J Nanobiotechnol*. 2022;20(1):222. doi:10.1186/s12951-022-01402-z