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Review Article

NANOMEDICINE AND GENE-BASED THERAPEUTIC STRATEGIES FOR NEURODEGENERATIVE DISEASES: A COMPREHENSIVE REVIEW

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ABSTRACT

Parkinson disease is a highly progressive condition that affects working of brain. it damages substantia nigra a nerve, which contains dopamine producing neurons. The damage leads to tremors, rigidity, slowing of movements, stiffness in body and problems in posture. Current treatments approches on to manage symptoms. They include medications, therapies and surgeries. These treatments may result in fluctuating symptoms, side effects and disease progression The authors reviewed the developing field of nanomedicine as a hopeful option for the treatment of Parkinson's disease. They highlighted its ability to address the weakness of traditional therapies. Nanomedicine uses nanoparticles for specific drug delivery these tiny particles are small enough to cross the blood brain barrier and deliver treatments directly to the affected areas in the brain. There are different types of nanoparticles such as lipids- based, polymeric, metallic, and carbon- based have shown promise for treating parkinsion's disease. Additionally, systems like liposomes, nanogels, dendrimers, and solid lipid nanoparticles can provide controlled and extended release for treatments. The improves their effectiveness and reduce side effects The review offer all insights into parkinson's disease explaining the root Causes of neuron (nerve) damage, the role of alpha – synuclein, and the disruption of dopamine pathways. It also discusses how gene therapy can be used as with nano medicine for better results.

KEYWORDS: Nanomedicine, Nanoparticles, Neuron, Neurodegenerative Disorder, Parkinson's Disease.

Introduction

Neurodegenerative conditions present a massive challenge to public health, primarily due to the complex immune responses they trigger within the central nervous system. While these immune pathways are essential for clearing out necrotic debris, managing viral threats, and facilitating tissue repair, they also carry a significant risk. When this activation goes unchecked, it can actually drive the progression of ischemia, infections, and various immune-mediated pathologies. Essentially, Neurodegeneration involves a slow, persistent decline of neurons and axons. This gradual breakdown interferes with normal cellular activities and eventually results in irreversible cell death[1].

The immune system's role in the brain is often a balance between protection and destruction:

- Regenerative Functions: Focusing on cellular repair and the removal of harmful necrotic cells.
- Pathological Consequences: Where prolonged activation contributes to ischemia and further neuronal decay.
- Cellular Failure: The end result of progressive axonal damage and functional abnormalities.

Table 1: Benefits and Outcomes

Beneficial Processes	Pathological Outcomes
Tissue regeneration and repair	Ischemia and immune-mediated disorders
Removal of necrotic cells	Acceleration of neurodegeneration
Limitation of viral infections	Total cellular demise

This ensures symptoms stem from the degeneration stage, beginning with a loss of memory, complete loss of ability to function as a normal healthy person. the three main neurodegenerative disorder are identified as[2].

- (AD) Alzheimer's Disease
- (PD) Parkinson's Disease
- (ALS) Amyotrophic lateral sclerosis

These diseases are interlinked closely to environmental cues, dysfunction of immune system, affects the natural ageing process, and an individual's unique genetic profile. These factors work to influence however; the disease develops and progress over the time[3]. Alzheimer's Disease (AD) has become a global health issue; it is currently impacting more than million individuals globally. Unfortunately, this figure is on a steady trajectory. This surge is driven by a combination of factors, including longer lifespan expectance, hereditary response and various environmental factors experts projected that the number of people living with AD will reach about 152 million by the year 2050.

Global impact and Projections

The rapid increase in AD cases reflects a rapid shift in global demographics and health risks Longevity: - as the average of lifespan increase, the period of exposure to age – chances & risk related neurodegeneration also increase[4]. The rising prevalence of these conditions is always set-to trigger a massive global economic crisis in the future. While in today's time Alzheimer's is a main concern, Parkinson's Disease (PD) also carries a same concern , data of Parkinson's indicates that roughly 10 million people globally are living with PD the data includes approximately one million in the United States[5]. For these individuals, the burden is twofold: they face a total disruption of their daily lives and a crushing financial worth form medical expenses , in the U.S. alone, the annual economic impact of PD is estimated about nearly $52 Billion. These disorders begin with the abnormal buildup and clustering of host proteins, which lead to compromised blood flow, the breakdown of tissue stability, and significantly immune- driven damage[6,7]. The brain is protected by a biological barrier that prevents most therapeutic substance form entering into brain. The restriction is maintained by blood vessels cells that are fused together with extreme tight space no gaps for molecules to leak through. These cells have very low tendency to absorb external materials and are packed with proteins that actively pump drugs back out into the bloodstream as soon as they try to enter in to the barrier to cross membrane. To pass layer of defense, high concentrations of specialized enzymes chemically neutralize medicines before they can reach to brain tissue, making it possible for both large and small drug compounds to pass form the blood to the brain. This challenge of crossing the (BBB) Barrier could potentially overcome the use o novel therapeutic nano- delivery systems[3].

Neurodegenerative Diseases

Neurodegenerative diseases represent a diverse group of conditions where the central nervous system (CNS) slowly and steadily breaks down. Doctors typically categorize these based on a patient's symptoms, such as changes in behavior, memory loss, or common movement difficulties like tremors and balance issues. On a cellular level, this decline happens because neurons stop working correctly and eventually die due to several "stressors," including internal inflammation, chemical imbalances (oxidative stress), and failures in the cell's natural recycling and waste-disposal systems[8]. The most frequent issues involve the abnormal clumping of specific proteins like tau, amyloid, and alpha synuclein, which form the unique "fingerprints" doctors look for when identifying a specific disease[8]. A major challenge in treating these disorders is that while toxic proteins begin building up early on, visible symptoms often don't appear until much later. By the time a diagnosis is made, a patient might even be suffering from more than one disease process simultaneously the most frequent issues involve the abnormal clumping of specific proteins like tau, amyloid, and α-synuclein, which form the unique "fingerprints" doctors look for when identifying a specific disease[9]. Diagnosis is further complicated because we lack clear "biomarkers"—biological red flags—except in rare cases where a specific genetic mutation is found[10]. In Alzheimer's Disease, these protein clumps—known as plaques and tangles—typically gather in the brain's outer layer (the neocortex). In Parkinson's Disease, different clumps called alpha synuclein inclusions are found in similar areas[11]. Unlike a viral infection where the "invader" is foreign, these clumps are made of the body's own proteins that have folded into abnormal, sticky shapes. These proteins grow and spread through the brain like a chain reaction. However, new treatments, such as advanced nano medicines and gene therapies, are being designed to stop these proteins from clumping, moving between cells, or being released in the first place, potentially halting the disease instead of just masking the symptoms[9,12]. Alzheimer's (AD) and

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Parkinson's (PD) are the most common neurodegenerative conditions, representing a major portion of brain-related health issues worldwide. These disorders can stem from inherited genetic traits or appear spontaneously due to how a person's genes react to their environment. In Parkinson's, research links the disease to genes that control how the body processes foreign chemicals and how specific "dopamine" neuron's function. On the other hand, a specific variation of the APOE gene is a well-known risk factor for developing Alzheimer's (Figure 1)[6,7].

Patho Physiology and Symptoms of Parkinson's Disease

Unlike other neurological conditions that affect broad areas, Parkinson's Disease (PD) targets a specific, well-defined group of neurons. This focus has allowed researchers to develop effective animal models and gain a deep understanding of how dopamine-producing cells grow and survive[13]. The disease primarily stems from damage in the substantia niagra, which leads to a loss of vital neurotransmitters and the breakdown of connecting fibers in the brain. This damage triggers a transition from motor malfunctions to non-motor issues[13-15]. Interestingly, symptoms often remain hidden until approximately 60% of these specialized dopamine neurons are lost, resulting in an 80% drop in dopamine levels[16,17]. Early signs typically include physical tremors, rigidity, and slow movement, alongside psychological challenges like anxiety and depression (Table 1)[18].

Genetic Drivers: SNCA and LRRK2

The genetic foundations of PD began with the discovery of mutations in the *SNCA* gene, which carries the instructions for the protein α-synuclein[19]. Research shows that having too many copies of this gene leads to an overproduction of α-synuclein, which becomes toxic to brain cells[20].

Another major player is the *LRRK2* gene; its most common mutation, *Gly2019Ser*, is a leading cause of both inherited and random cases of PD globally. This mutation causes the gene's enzymatic core to become overactive, damaging neurons. Because of this specific mechanism, modern gene therapies are currently being developed to target and inhibit this overactive kinase domain[21,22].

Protective Genes: DJ-1 and PARK7

The *PARK7* gene produces a protein called DJ-1, which normally acts as a shield against oxidative stress. In many PD patients, this protein is under-expressed, leaving neurons vulnerable to damage[23,24].

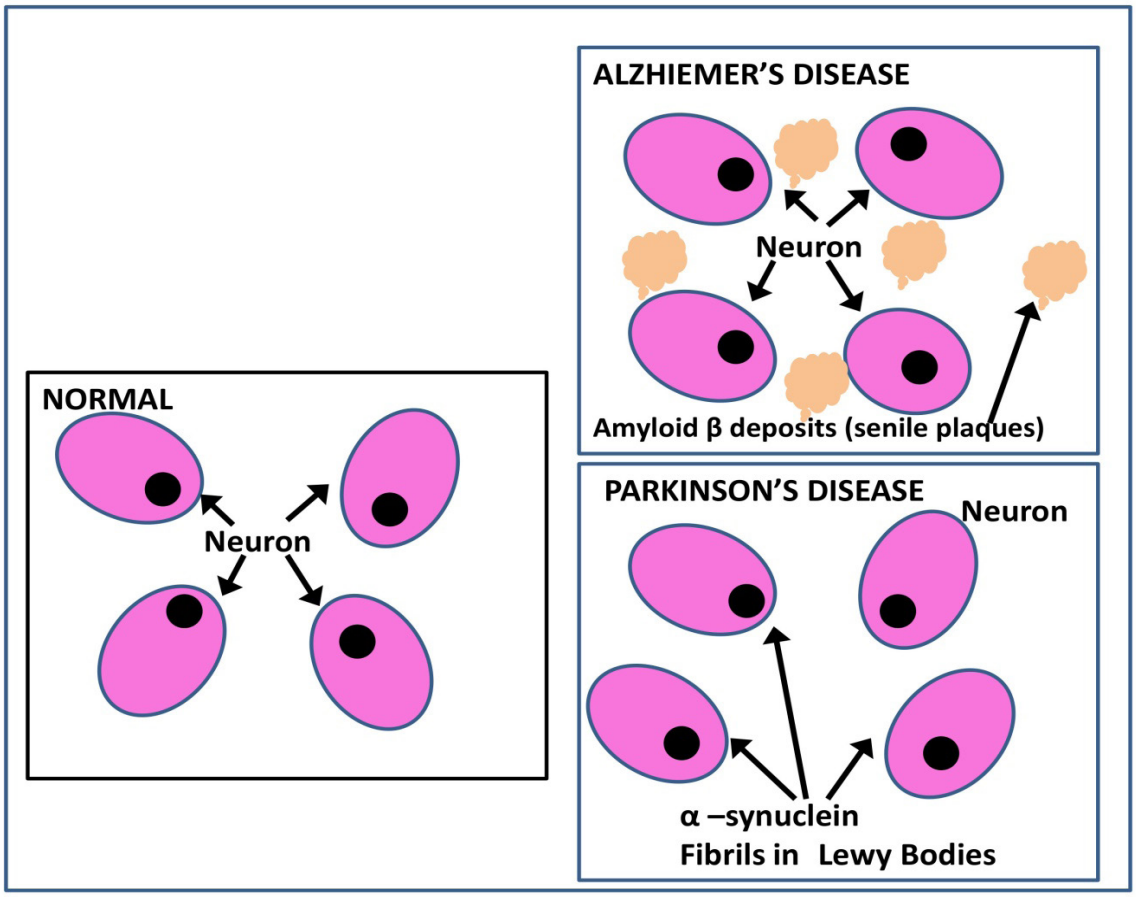

Figure 1: The appearance of amyloid plaques in Alzheimer's disease and α-synuclein inclusions in the neurons in Parkinson's disease

Because of its protective nature, *PARK7* is a primary candidate for gene therapy. Experiments in rat models have shown that increasing DJ-1 levels can successfully preserve dopamine neurons[25]. Researchers are even exploring specialized "fusion cells" designed to cross the blood-brain barrier to deliver these protective effects directly to the brain[26].

Protein Recycling and the UCHL1 Gene

The body's system for recycling old proteins, known as the ubiquitin-proteasome system (UPS), is vital for brain health. Mutations in the *UCHL1* gene disrupt this system, causing a shortage of "free" ubiquitin and leading to nerve fiber decay and movement instability[27,28]. While some mutations in this gene cause disease, others—like the *S18Y* variant—actually provide antioxidant protection and lower a person's risk for PD. This makes *UCHL1* a promising target for both nanomedicine and genetic intervention[29,30].

Cell Survival Regulators: PTEN and PINK1

The *PTEN* gene plays a dual role: it regulates cell growth but, when overactive, can trigger a "suicide command" (apoptosis) that kills neurons[31,32]. To counter this, the body uses PINK1, a protein that protects mitochondria and prevents cell death caused by excessive PTEN[33]. Similarly, the *PARK2* gene produces Parkin, which acts as a quality control manager for mitochondria. When Parkin fails, damaged mitochondria pile up, causing oxidative stress and the eventual death of the neurons responsible for movement[34,35].

The Future of Personalized Nano medicine

Understanding these specific genetic blueprints is essential for creating effective treatments. By using nanoparticles to carry therapeutic genes, scientists can now aim to "turn off" harmful overactive genes or "turn on" protective ones like Parkin. Because every patient's genetic makeup is different, this shift toward "personalized medicine" offers a way to treat the root cause of Parkinson's while significantly reducing the side effects associated with traditional drugs[34,35].

Overview and Pathological Mechanisms of Alzheimer's Disease

Alzheimer's Disease (AD) is a leading, irreversible cause of dementia, characterized by a steady decline in memory and cognitive abilities. It represents between 60% and 80% of all dementia cases worldwide .[36] The biological foundation of this decay involves the buildup of amyloid-beta (Aβ) plaques outside of cells and neurofibrillary tangles inside them, both of which lead to toxic effects and the loss of vital synaptic connections.[37] A primary driver of this process is the way the amyloid precursor protein (APP) is broken down by specific enzymes—β-secretase and γ-secretase—into harmful Aβ peptides. Because this pathway is so central to the disease, researchers are focusing on developing inhibitors for various enzymes, such as caspases and δ-secretase, to halt the production of these toxic proteins[38,39].

The Role of PSEN1 in Familial Alzheimer's

Mutations in the PSEN1 gene are the most frequent cause of inherited, or familial, Alzheimer's (FAD). This gene provides the instructions for presenilin-1, a key component of the γ-secretase enzyme that slices proteins like APP[40]. When this process goes wrong, it produces specific versions of amyloid (Aβ40 and Aβ42). The Aβ42 version is particularly "sticky" and hydrophobic, causing it to clump together and form the plaques seen in patients' brains[41]. Beyond protein clumping, mutations in *PSEN1* may cause a loss of the protein's normal functions, which are essential for learning, memory, and keeping neurons alive as the brain ages[40].

Rare Mutations and the Impact of PSEN2

While *PSEN1* mutations are common in familial cases, *PSEN2* mutations are much rarer, with fewer than 40 known variations. These mutations can lead to a wide range of conditions, from early and late-onset Alzheimer's to fronto temporal dementia and even certain non-neurological diseases like breast cancer[42,43]. Although *PSEN2* follows a similar pathological path to *PSEN1* by triggering amyloid aggregation, it generally does so to a lesser degree[44]. Nevertheless, both *PSEN* genes are considered high-priority targets for advanced treatments using nanomedicine and gene-based therapies.

Genetic Risk Factors: The Apoe Connection

The *ApoE* gene is normally responsible for transporting lipids and repairing injuries within the brain. However, certain variations of this gene significantly increase a person's risk for AD[45]. While most people carry the ϵ3 version, those with the ϵ4 allele face a much higher risk of cognitive decline and amyloid buildup in the brain's blood vessels[46]. Mutations in *ApoE* disrupt many critical brain functions, including how the brain uses glucose, manages inflammation, and clears out amyloid clumps. When *ApoE* fails to function correctly, it triggers a cascade of toxic events that damage synapses and lead to widespread neurodegeneration[45].

Nanoparticles and Nanomedicine

The Versatility and Design of Nanomedicine

Integrating nanoscale particles into medical practice offers a transformative approach to treating complex diseases. These particles are highly valued for their specific physical traits—including size, geometry, and surface texture—which can be precisely engineered to meet clinical needs[47,42].

Noble Metal Nanoparticles and Their Uses

The safety and success of nanoparticles (NPs) depend on their physical and chemical makeup. By adding polymers or special "targeting" molecules to their surface, scientists can

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make these particles stick better to drugs or genes and ensure they go to the right cells [48] Noble metals like gold, silver, platinum, and palladium are popular choices because they have unique light-related and biological strengths[49]. Gold nanoparticles are particularly easy to customize for medical use. They have shown promise in treating various conditions, from skin ulcers to viral infections, and can even help detect protein clumps related to Alzheimer's[50,51]. While silver is great for fighting germs and viruses in wounds, it tends to clump together if not modified[52]. Palladium Used in Dental and Electrical Tools, But When Combined with Gold and Natural Compounds Like Quercetin, It May Help the Brain "Clean itself" In Alzheimer's Cases. It acts as a powerful antioxidant, some platinum- based cancer drugs can be tough on the nervous system (Figure 2)[49,53].

Specialized Elements: Selenium and Silica

Selenium is a vital nutrient that helps protect the body against heart disease, joint pain, and brain disorders like Alzheimer's[54,55]. As nanoparticles, selenium is less toxic and easier for the body to use compared to standard forms, making it a popular choice for boosting the effects of other drugs[56]. Similarly, "mesoporous" silica nanoparticles are gaining attention because they are filled with tiny holes or pores. This porous structure provides a huge amount of surface area, allowing them to carry both drugs and genes at the same time to improve treatment[57,58].

Magnetic and Carbon-Based Nanoparticles

Iron oxide particles, or magnetic nanoparticles (MNPs), are widely used because they are stable, safe, and can be guided through the body using external magnets—a process called magnetoception[59]. They are excellent for clear medical imaging (like MRIs) and targeted drug delivery, though they must be coated to prevent them from clumping or causing unwanted chemical reactions[60]. Other materials like "Quantum Dots" have amazing glowing properties for imaging but can be toxic unless they are carefully coated[61]. Carbon nanotubes are another option that can easily enter cells, but they require significant modification to make them safe and dissolvable in the body[62].

Polymers and Lipids in Brain Therapy

Polymeric systems have improved over time, especially "cationic" polymers that naturally bond with genetic material. These materials must be able to break down safely in the body[61]. Dendrimers, which have a tree-like structure, are often used to stabilize metal particles like gold[63]. One specific polymer, PLGA, is already FDA-approved and works well with gold for drug delivery, especially when modified to stay in the blood longer[64]. Additionally, liposomes—tiny fat bubbles—are frequently used to carry medicine and have shown positive results in Alzheimer's animal studies (Figure 3)[65].

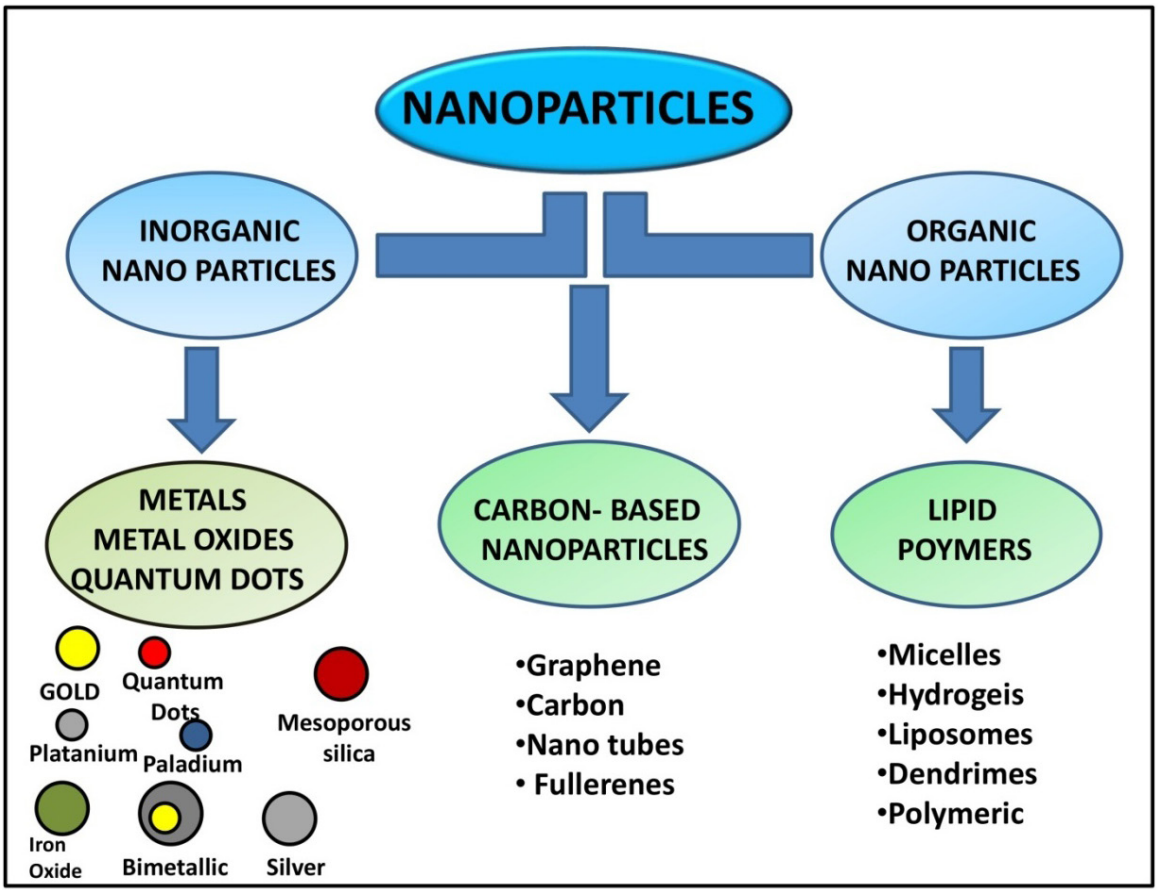

Figure 2: Broad classes of Nanoparticles showing those commonly used in nanomedicine

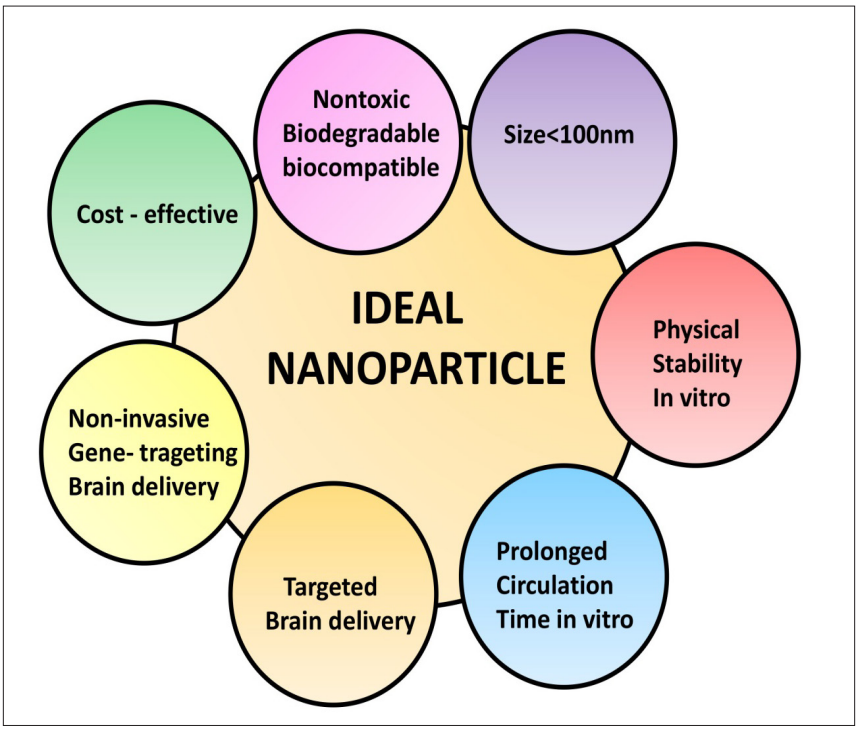

Figure 3: Ideal criteria required for the development of a safe and efficient nanoparticle for use in Nanomedicine

Choosing the Best Nano system

In many cases, inorganic nanoparticles (like metals or silica) are preferred over organic ones because they are easier to make, more stable, and can work for both diagnosis and treatment at the same time. While all these technologies show great potential for treating brain disorders like Alzheimer's and Parkinson's, the specific properties of each particle like size and stability must be carefully planned to ensure they are effective and safe[66].

Emerging Therapeutic Strategies for Atypical Parkinsonism

Progressive Supranuclear Palsy (PSP) and Corticobasal Degeneration (CBD)

Progressive Supranuclear Palsy (PSP) is classified as an a kinetic-rigid syndrome under the umbrella of parkinsonism, fundamentally driven by the intracellular accretion of hyperphosphorylated tau protein (MAPT). This pathological accumulation disrupts the integrity of microtubules, which is a primary mechanistic driver of neuronal dysfunction[67]. Pathologically, the 4R-isoform of tau predominates, leading to the formation of neurofibrillary tangles and tufted astrocytes—morphological features that define the disease's landscape[68-70]. The clinical presentation of PSP is notably diverse. Currently, no histological markers provide a definitive separation between PSP phenotypes, requiring specialists to rely on the anatomical distribution of tau deposits for differentiation[70,71]. Consequently, early diagnostic precision is essential, not only for establishing a patient's long-term prognosis but also for facilitating participation in novel therapeutic trials[68]. While the exact etiology remains a mystery, current research is intensely focused on triggers such as genetic predisposition and oxidative stress[68,72].

Targeting Neuro inflammation and Oxidative Stress

In the central nervous system, microglia function as the primary immune regulators[73]. Evidence suggests that microglial activation initiates the p38-mitogen activated protein kinase (p38-MAPK) pathway, which subsequently accelerates tau protein phosphorylation and clustering[73]. Furthermore, researchers have noted a link between tau accumulation and the expression of receptors like TLR4 and CX3CR1, identifying these as potential targets for future pharmacological intervention[74]. The enzyme 5-Lipoxygenase (5-LO) also plays a pivotal role in the inflammatory cascade; its suppression in animal models has led to reduced tau levels and measurable cognitive gains[75,76]. Similarly, benfotiamine (BFT)—a lipophilic thiamine derivative—is being studied for its capacity to stimulate the Nrf2/ARE pathway, thereby dampening inflammation markers such as TNFα and COX-2[77,78]. Additionally, antioxidants like Co-enzyme Q10 have demonstrated potential in short-term studies, where they appeared to improve metabolic activity and clinical rating scores[79].

RNA Modulation and Kinase Inhibition

Innovative approaches to PSP are now targeting the molecular foundations of the disease through ribonucleic acid (RNA) modification. Antisplicing oligonucleotides (ASOs) are being designed to stabilize RNA structures and prevent the buildup of toxic tau proteins[80]. Preclinical

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research indicates that MAPT ASOs significantly lower tau concentrations and protect against neuronal loss[81,82]. Simultaneously, kinase inhibition is a cornerstone of current research. Activating the phosphorylated endoplasmic reticulum kinase (PERK) pathway serves as a defense against misfolded proteins; for instance, the activator CCT020312 has demonstrated neuroprotective properties in P301S mouse models[83,84]. Furthermore, Rho-associated coiled-coil-containing protein kinase (ROCK) inhibitors, such as Fasudil, are currently in Phase 2 trials to monitor their effect on neurodegeneration markers like neurofilament light chain[85,86].

Multiple System Atrophy (MSA) and α-Synuclein

Multiple System Atrophy (MSA) is a fatal neurodegenerative disorder characterized by rapid progression and a limited life expectancy of roughly 6 to 10 years[87]. The disease is defined by the abnormal accumulation of α-synuclein, primarily within the cytoplasm of oligodendroglia, forming glial cytoplasmic inclusions (GCIs)[88,89]. These GCIs also incorporate other secondary proteins, including ubiquitin and p62.[90,91]. Research into MSA focuses heavily on blocking or neutralizing these α-synuclein clusters. Anle 138b is an oral inhibitor that has shown success in reducing GCI density and restoring motor functions in animal models[92,93]. Furthermore, immunotherapy remains a major area of interest; vaccines like PD01 and PD03 have proven safe in early human trials and are capable of eliciting a robust antibody response against α-synuclein[94,95].

Stem Cell Therapy and Regenerative Medicine

Mesenchymal stem cells (MSCs) derived from bone marrow or adipose tissue represent a significant therapeutic frontier[96]. These cells can release immunomodulating cytokines and neuroprotective factors that inhibit cell death and encourage proliferation[97]. In patients with MSA, the administration of MSCs via intravenous or intraarterial routes has been associated with a slower rate of disease progression on the Unified MSA Rating Scale (UMSARS) [98]. For PSP, research suggests that MSCs can cross the blood-brain barrier and release critical neurotrophins like BDNF[99]. Although clinical trials have confirmed the safety of these stem cell procedures, the observed clinical gains—such as improvements in the PSP Rating Scale (PSPRS)—have often been temporary, highlighting the necessity for further investigation into long-term efficacy[100,101].

Metabolic Regulation and Myeloperoxidase Inhibition

Current data suggests that insulin resistance in the putamen and oligodendrocytes may contribute significantly to the neurodegenerative process in MSA[102]. Clinical trials with intranasal insulin have shown that treated patients often perform better in motor and cognitive tests[103]. Moreover, glucagon-like peptide 1 (GLP-1) analogs are being studied for their ability to mitigate insulin resistance and preserve neuronal health[104]. Another therapeutic target is Myeloperoxidase (MPO), an enzyme that is highly expressed in areas of neurodegeneration. Inhibiting MPO has been shown to reduce microglial activation and neuroinflammation[105]. The drug Verdi prestart is currently in Phase 3 trials, aiming to establish its efficacy in slowing MSA progression[106,107].

Comparative Summary of Experimental and Clinical Therapeutics

The following table provides a synthesized overview of emerging pharmacological and cellular interventions currently under investigation for Progressive Supranuclear Palsy (PSP), Corticobasal Syndrome (CBS), and Multiple System Atrophy (MSA).

Advanced Therapeutic Modalities for Parkinson's Disease

Personalized Paradigms in Device-Aided Therapy

The evolution of personalized medicine in Parkinson's Disease (PD) focuses on tailoring interventions to a patient's unique genetic markers and clinical phenotype. While motor and non-motor symptoms vary significantly among individuals, the lack of definitive biomarkers means that treatment selection—ranging from pharmacological adjustments to surgical interventions—remains largely dependent on clinical staging and patient-specific comorbidities[108,109].

Table 2: Emerging Therapeutic Pipeline for Atypical Parkinsonism

Mechanism of Action	Agent / Strategy	Phase / Status	Primary Clinical Findings	Reference
Inflammatory Modulation	5-LO Inhibition	Pre-clinical	Suppressing 5-lipoxygenase led to a marked reduction in tau levels and measurable cognitive gains in models.	[75, 76]
	Benfotiamine (BFT)	Pre-clinical	This thiamine derivative activated the Nrf2/ ARE pathway, providing neuroprotection and lowering glycated tau.	[77, 78]
	Tolfenamic Acid (TA)	Phase IIa	Assessing the safety and efficacy of reducing total cerebral tau distribution via oral administration.	[77, 79]

Metabolic & Oxidative Support	PERK Activation	Pre-clinical	Pharmacological activators (CCT020312) improved motor function and reduced phosphorylated tau in P301S models.	[83, 84]
	Coenzyme Q10	Phase II	Trials showed modest metabolic stabilization and rating scale (PSPRS) improvements, though long-term data were mixed.	[79, 108]
	NBMI (Chelator)	Phase IIa	Investigating the impact on both motor and non-motor symptoms in patients with PSP and MSA.	[109]
Genetic & RNA Targets	Antisense Oligonu-cleotides (ASO)	Phase I	Successfully reduced tau mRNA and protein levels in the CSF of human participants; currently monitoring safety.	[81, 82]
	O-GlcNAcase Inhibition	Phase I	Demonstrated a safe profile in human volunteers; evaluating its capacity to suppress tau aggregation in the CNS.	[110-112]
Kinase & Protein Regulation	ROCK Inhibition (Fasudil)	Phase II	Monitoring safety and changes in neurodegeneration biomarkers, particularly neurofilament light chain (NfL).	[85, 86]
	GSK-3β Blockade (Tideglusib)	Clinical	Designated as an orphan drug; trials confirmed safety but failed to meet primary clinical efficacy endpoints.	[113, 114]
	Nilotinib	Pre-clinical / II	Effective in reducing tau in models, but did not produce significant clinical benefits in recent human AD trials.	[115, 116]
Immuno therapy	α-Synuclein Vaccines	Phase I	Vaccines (PD01/PD03) generated a robust and sustained IgG antibody response against pathological synuclein in MSA.	[94, 95]
Regenerative Medicine	Mesenchymal StemCells (MSCs)	Phase I / II	Stem cell delivery suggested clinical stabilization and slowed UMSARS progression, though effects were temporary.	[98-101]
Insulin & Enzyme Targeting	Intranasal Insulin	Phase II	Participants treated with insulin performed significantly better in motor and cognitive assessment scales.	[102, 103]
	Verdiperstat (MPO Inhibitor)	Phase III	Evaluating whether blocking myeloperoxidase can successfully slow the overall disease progression of MSA.	[106, 107]

Current diagnostic frameworks, such as those established by the Parkinson's Progression Markers Initiative (PPMI), categorize patients into motor-predominant or diffuse malignant subtypes to better predict disease trajectory and treatment response (Table 2)[110,111].

Deep Brain Stimulation (DBS) and Adaptive Technology

Deep Brain Stimulation (DBS) has transitioned from a salvage therapy to a gold-standard intervention for advanced motor complications. By implanting electrodes in the subthalamic nucleus (STN) or globus pallidus internus (GPi), clinicians can modulate dysfunctional neural circuits[112]. The introduction of directional leads has further refined this approach, allowing for precise steering of the current to avoid side effects such as dysarthria or cognitive decline[113,114]. Moreover, the advent of adaptive DBS (aDBS) allows for closed-loop stimulation, where the device senses local field potentials (beta oscillations) and adjusts the electrical output automatically to match the patient's real-time physiological state[115,116].

Infusion Therapies: LCIG and Apomorphine

Patients with severe gastric motility issues, Levodopa-Carbidopa Intestinal Gel (LCIG) provides a continuous dopaminergic delivery system. By infusing the gel directly into the jejunum, LCIG bypasses the stomach and maintains

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stable plasma levels, which significantly reduces "off-time" and troublesome dyskinesia[117,118]. Similarly, subcutaneous apomorphine infusion offers a less invasive alternative for managing motor fluctuations. These "device-aided therapies" are particularly effective for patients over 70 who maintain a good response to L-dopa but suffer from medication-related complications[119,120].

Ablative Procedures and Focused Ultrasound (MRgFUS)

While DBS is adjustable, ablative surgeries like MR-guided Focused Ultrasound (MRgFUS) offer a non-invasive, "incisionless" alternative for tremor suppression. MRgFUS utilizes high-intensity ultrasound to create targeted thermal lesions in the thalamus[121]. This approach is ideal for patients who are averse to implanted hardware or have contraindications for traditional surgery. However, unlike DBS, the effects of MRgFUS are permanent, necessitating extreme precision to avoid irreversible speech or gait disturbances[122,123].

Biological Frontiers: Cell and Gene Therapy

iPSC-Derived Cellular Replacement

Regenerative medicine for PD has reached a milestone with the use of Induced Pluripotent Stem Cells (iPSCs). Unlike older fetal tissue transplants, iPSCs can be derived from the patient's own skin or blood cells, reducing the risk of immune rejection[124]. These cells are reprogrammed into midbrain dopaminergic neurons and surgically transplanted into the putamen to restore the brain's natural dopamine production[125]. Early human trials have shown that this biological replacement can improve quality of life and potentially slow the progression of motor symptoms (Table 3) [126,127].

Targeted Gene Delivery via Viral Vectors

Gene therapy aims to turn the striatum into a self-sustaining dopamine production site. Utilizing Adeno-associated virus (AAV) vectors, researchers deliver genes such as Aromatic L-amino acid decarboxylase (AADC) directly into the brain tissue[128]. This increases the efficiency of oral L-dopa conversion and provides a more consistent therapeutic effect. Recent studies have demonstrated that higher doses of these viral vectors correlate with increased "on-time" and improved motor scores in advanced PD patients[129,130].

Exosome-Mediated Transport

Biological nanocarriers, particularly mesenchymal stem cell-derived exosomes, are emerging as superior alternatives to synthetic systems due to their innate biocompatibility and minimal immunogenicity[131]. These biogenic vesicles bypass the blood-brain barrier (BBB) primarily through transcytosis, utilizing the cell's internal transport machinery to deliver therapeutic cargo[132]. In Parkinson's Disease (PD) research, exosomes are being engineered to carry small interfering RNA (siRNA), which specifically targets and silences the $SNCA$ gene. This biological delivery system effectively protects the RNA from enzymatic degradation while ensuring high-precision "knockdown" of α-synuclein production within the striatal neurons[133,134].

This table evaluates the mechanical and biological platforms used to bypass the Blood-Brain Barrier (BBB) and provide sustained therapeutic effects (Table 3).

Table 3: Comparative Analysis of Advanced Drug Delivery Systems in PD

Delivery System	Primary Mechanism	Key Clinical Advantage	Reference
Exosomes	Biogenic transcytosis	Zero immunogenicity and natural BBB penetration.	[131, 132]
MRgFUS	Acoustic tight-junction disruption	Non-invasive, site-specific, and reversible BBB opening.	[135, 137]
LCIG (Infusion)	Continuous jejunal delivery	Stable plasma levels; bypasses gastric motility issues.	[138, 140]
Nanoparticles	Receptor-mediated endocytosis	Targeted delivery of labile payloads (siRNA/ Peptides).	[133, 145]
AAV Vectors	Viral-mediated transduction	Long-term, localized enzymatic upregulation.	[141, 143]

Focused Ultrasound (FUS) for BBB Opening

Magnetic Resonance-guided Focused Ultrasound (MRgFUS) represents a paradigm shift from permanent tissue ablation to temporary, non-invasive BBB disruption. By utilizing low-intensity ultrasound waves in combination with systemic microbubbles, the tight junctions of the BBB can be opened transiently (4–6 hours) at specific coordinates like the substantia nigra[135]. Clinical trials have demonstrated that this technique allows for the localized concentration of macromolecules—such as gene vectors or neurotrophic factors—that would otherwise be too large to penetrate the CNS. This site-specific approach minimizes systemic exposure and protects healthy brain regions from unnecessary therapeutic payloads[136,137].

Implantable and Infusion Systems

Long-term motor complications in advanced PD are often managed through continuous dopaminergic stimulation via Levodopa-Carbidopa Intestinal Gel (LCIG) and Apomorphine subcutaneous infusion. LCIG utilizes a percutaneous endoscopic gastrostomy-jejunal (PEG-J) tube to deliver medication directly to the jejunum, avoiding gastric emptying issues and ensuring stable plasma levels[138]. In contrast, apomorphine infusion provides a less invasive subcutaneous route, effectively reducing "off-time" and dyskinesia by up to 50–80%. While LCIG is often preferred for patients with severe dysphagia, apomorphine offers a more manageable profile for younger, active patients despite potential skin site reactions[139,140].

Table 4: Molecular Targets and Therapeutic Payloads for Novel PD Interventions

Therapeutic Target	Payload Type	Biological Impact	Reference
$SNCA$ mRNA	siRNA / shRNA	Silences production of toxic alpha synuclein s protein.	[133, 154]
AADC Enzyme	AAV-hAADC Gene	Enhances conversion of L-dopa to dopamine in the striatum.	[141, 142]
NLRP3 Inflammasome	Synthetic modulators	Reduces microglial-driven neuroinflammation.	[144, 146]
TFEB Regulator	miRNA / Nanocarriers	Activates autophagy for protein aggregate clearance.	[147, 148]
GDNF / BDNF	Neurotrophic Factors	Stimulates axonal regrowth and neuronal survival.	[150, 152]

Molecular Pathways and Novel Payloads

Dopaminergic Pathway Enhancement

To address the diminishing efficacy of oral medications, gene therapy strategies focus on upregulating the Aromatic L-amino acid decarboxylase (AADC) enzyme. Using Adeno-associated virus (AAV) vectors, the $hAADC$ gene is delivered directly into the putamen[141]. This intervention turns striatal cells into "dopamine factories," enhancing the brain's ability to convert exogenous levodopa into functional dopamine. Long-term follow-up studies confirm that AAV2-hAADC expression remains stable for over four years, providing sustained motor improvements and reducing the daily requirement for oral L-dopa[142,143].

Targeting Neuroinflammation and the NLRP3 Inflammasome

Chronic neuro inflammation in PD is largely driven by the overactivation of the NLRP3 inflammasome within microglia. This complex triggers the release of pro-inflammatory cytokines like IL-1β and IL-18, leading to dopaminergic cell death[144]. Advanced nanomedicine utilizes nanoparticles to scavenge Reactive Oxygen Species (ROS) and regulate calcium flux, which are key triggers for NLRP3 activation. By delivering synthetic inflammasome modulators or specific miRNAs directly to activated microglia, these nano systems effectively "cool down" the inflammatory environment and protect neighboring neurons from secondary degeneration (Table 4) [145,146].

Modulating Autophagy via Transcription Factor EB (TFEB)

Transcription Factor EB (TFEB) is recognized as the master regulator of the Autophagy-Lysosomal Pathway (ALP). In PD, TFEB dysregulation leads to the toxic buildup of α-synuclein. Therapeutic strategies now employ nanocarriers to overexpress TFEB, which binds to the Coordinated Lysosomal Expression and Regulation (CLEAR) network[147]. This activation enhances lysosomal biogenesis and autophagic flux, promoting the clearance of misfolded protein aggregates and extending the survival of dopaminergic neurons in the substantia nigra[148,149].

Neurotrophic Factor Delivery (GDNF and BDNF)

Disease-modifying treatment aims to not only protect but also repair the nigrostriatal circuit through Neurotrophic

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Factors (NTFs) like GDNF and BDNF. GDNF is significantly more potent than BDNF in correcting motor deficits and stimulating axonal regrowth[150]. Current delivery research compares viral vectors, which offer long-term but invasive expression, with non-viral nanoparticle-mediated platforms. The use of cationic microbubbles triggered by focused ultrasound (FUS) has shown promising results in animal models, achieving high-titer GDNF expression without the risks associated with permanent viral integration[151,152].

RNA-Based Therapeutics and Gene Silencing

Precision "gene silencing" at the transcript level is achieved through siRNA and shRNA nanocarriers. These RNA molecules are designed to specifically target the $SNCA$ mRNA, blocking the translation of α-synuclein proteins before they can aggregate into Lewy bodies[153]. By utilizing non-invasive delivery routes, such as intranasal administration or FUS-targeted delivery, these nanotherapies achieve a significant "knockdown" of pathological protein production. This substrate reduction strategy is critical for halting the prion-like spread of neurodegeneration across neural networks[154,155].

Molecular Pathways Explored via Novel Delivery

Alpha-Synuclein Proteostasis and Aggregation Inhibition

The pathogenic conversion of α-synuclein from its native, disordered monomeric state into insoluble, cross-β sheet fibrils constitutes the primary biochemical hallmark of Lewy body pathology. This misfolding trajectory is largely dictated by the non-amyloid-beta Component (NAC) region, specifically residues 61–95, where hydrophobic clusters initiate the primary nucleation of protofibrils[156]. Advanced nanotherapeutic interventions utilize functionalized gold nanoparticles (AuNPs) or carbon-based quantum dots designed to dock with the NAC hydrophobic pocket. This interaction creates a steric "shield" that effectively halts the template-driven recruitment of endogenous monomers[157], Simultaneously, nanocarriers are being developed to augment chaperone-mediated autophagy (CMA). By delivering specific peptide enhancers that increase the affinity between the KFERQ-like motif on α-synuclein and the LAMP-2A receptor on lysosomal membranes, these systems accelerate the clearance of pre-fibrillar oligomers before they can cause mitochondrial membrane permeabilization[158,159].

LRRK2 Kinase Signaling and Lysosomal Dysfunction

The G2019S mutation in the Leucine-rich repeat kinase 2 (LRRK2) gene represent a toxic gain-of-function that triggers aberrant kinase activity. This hyperactive state results in the over-phosphorylation of Rab GTPases (specifically Rab8, Rab10, and Rab12), which fundamentally disrupts the retrograde transport of essential vesicles to the lysosomal compartment[160]. To counteract this, current molecular strategies utilize PEGylated lipid-based nano capsules to deliver highly selective LRRK2 kinase inhibitors across the blood-brain barrier. These inhibitors facilitate the restoration of lysosomal acidification and the reactivation of the v-ATPase pump, ensuring that proteolytic enzymes like Cathepsin D remain functional[161]. By clearing the accumulated autophagic vacuoles, these nano systems prevent the "cellular clogging" that traditionally precedes pro-apoptotic signaling in dopaminergic neurons[162].

The NLRP3 Inflammasome and Chronic Neuroinflammation

Neurodegeneration in the *substantia nigra* is exacerbated by the sustained activation of the NLRP3 inflammasome within the microglial population. This multiprotein complex—comprising the NLRP3 sensor, the ASC adapter, and pro-caspase-1—assembles in response to mitochondrial Reactive Oxygen Species (ROS) or phagocytosed α-synuclein[163]. The resulting activation leads to the pore-forming activity of Gasdermin D (GSDMD), facilitating the rapid secretion of potent pro-inflammatory cytokines IL-1β and IL-18[164]. Innovative nanomedicine platforms employ Cerium Oxide Nanoparticles (nanoceria), which mimic the catalytic activity of superoxide dismutase. By neutralizing the intracellular ROS levels at the source, these nanoceria inhibit the initial nucleation of the NLRP3 complex, thereby "deactivating" the microglial inflammatory phenotype and preserving the integrity of neighboring dopaminergic circuits[165,166].

GDNF-Mediated Ret Signaling and Neuronal Repair

The therapeutic delivery of Glial Cell-Derived Neurotrophic Factor (GDNF) is designed to engage the Ret receptor tyrosine kinase to initiate neuronal recovery. Upon the binding of GDNF to the GFRα1 co-receptor, Ret undergoes homodimerization and autophosphorylation, which subsequently triggers the PI3K/Akt and MAPK/ERK survival cascades[167]. These molecular pathways promote the expression of anti-apoptotic proteins and stimulate the compensatory sprouting of neurites. Given that GDNF is a 30 kDa homodimer unable to penetrate the BBB, functionalized polymeric nanocarriers or viral-mediated gene delivery are utilized to ensure high concentrations within the putamen. This strategy facilitates a molecular "re-innervation" of the striatum, potentially restoring the dopamine release architecture[168].

Conclusion and Future Perspectives

A clear step toward precision neuro medicine has been taken with the incorporation of nanotechnology into the therapeutic treatment of Parkinson's disease. According to this review's analysis, the engineering of functionalized nanocarriers—like exosomes and solid lipid nanoparticles—that enable the cite-specific delivery of molecular payloads is helping to identify the historical challenges of the blood-brain barrier. Because of their complicated genesis, delayed clinical presentation, and restricted medication accessibility

to the central nervous system, neurodegenerative illnesses continue to rank among the most difficult conditions to treat. This article shows how the combination of molecular neuroscience, gene therapy, and nanotechnology is changing the way that Parkinson's disease, Alzheimer's disease, and atypical parkinsonian disorders are treated. The blood–brain barrier has long been a problem, but recent developments in targeted ultrasound, RNA regulation, exosome-mediated transport, and nanoparticle engineering have all helped to overcome it. These methods change the paradigm of treatment from symptomatic relief to disease modification by enabling site-specific, persistent, and minimally invasive administration of therapeutic payloads. Future treatment success will rely on accurate patient categorization, combination medicines that target several disease pathways at once, and early diagnosis backed by reliable biomarkers. Personalized nano-enabled therapies have the potential to reduce, stop, or even reverse neurodegenerative diseases as precision neuro medicine develops. To sum up, the combination of molecular genetics, nanomedicine, and sophisticated delivery systems is a revolutionary step toward personalized and successful treatment plans for neurodegenerative illnesses, giving patients new hope and redefining the direction of neurological therapies.

Discussion

Atypical parkinsonian syndromes, Parkinson's disease (PD), Alzheimer's disease (AD), and other neurodegenerative diseases are the result of a complex interaction between genetic predisposition, protein misfolding, mitochondrial malfunction, and neuroinflammation. The upstream molecular processes that cause progressive neuronal loss are not addressed by conventional symptom-centric therapy, as this review demonstrates. Thus, three overlapping themes—pathological protein homeostasis, neuroimmune dysregulation, and barrier-limited medication delivery—are at the heart of the conversation. The abnormal accumulation of intrinsically disordered proteins, including tau, amyloid-β, α-synuclein, and AD, is a characteristic shared by PD, AD, PSP, and MSA. These proteins disseminate disease throughout anatomically related areas in a way similar to that of prion propagation. Traditional pharmacological methods do not stop this pathogenic spread; instead, they mainly alter neurotransmitter levels. Traditional pharmacological methods do not stop this pathogenic spread; instead, they mainly alter neurotransmitter levels. On the other hand, new nano-enabled platforms and RNA-based treatments show promise in lowering the production, aggregation, or intercellular transfer of hazardous species by acting at the transcriptional and post-translational stages. It has become clear that neuroinflammation is a primary cause of neurodegeneration rather than a subsequent effect. Through prolonged cytokine release and oxidative stress, chronic activation of microglia through pathways such NLRP3 inflammasome signaling, p38-MAPK, and TLR4 speeds up neuronal damage. Targeted delivery of anti-inflammatory payloads, such as antioxidant nanoparticles, kinase inhibitors, and miRNAs, provides a way to modify active microglia in a specific way without sacrificing vital immune surveillance. The blood-brain barrier's (BBB) restrictive nature is another significant issue that has been examined. Although evolutionarily protective, the BBB severely restricts the absorption of CNS drugs. A paradigm shift has been brought about by developments like exosome-based administration, receptor-mediated nanoparticle transport, and focused ultrasound-mediated BBB opening. By enabling temporary, targeted, and reversible BBB manipulation, these methods maximize therapeutic concentration at sick locations while minimizing systemic toxicity. Crucially, this review highlights the trend toward precision neuro medicine, in which individual molecular markers, illness subtype, and genetic alterations (e.g., SNCA, LRRK2, APOE, PSEN1) inform treatment plans. This individualized strategy has the potential to increase therapeutic efficacy while reducing side effects, which has previously hampered the development of neurodegenerative drugs.

Abbreviations

AADC: Aromatic L-amino acid decarboxylase

AAV: Adeno-associated virus

BBB: Blood-brain barrier

CNS: Central nervous system

FUS: Focused ultrasound

GBA: Glucocerebrosidase

GDNF: Glial cell-derived neurotrophic factor

iPSC: Induced pluripotent stem cell

LCIG: Levodopa-carbidopa intestinal gel

LRRK2: Leucine-rich repeat kinase 2

miRNA: MicroRNA

NLRP3: Nucleotide-binding oligomerization domain-like receptor protein 3

PD: Parkinson's disease

ROS: Reactive oxygen species

siRNA: Small interfering RNA

SNCA: Alpha-synuclein gene

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None

Conflict of Interest

None

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