Nanotechnology Advancement for Therapeutic Discovery for Neurodegenerative Disorders

Irum Waheed[1, 2,*], Aqsa Mahmood[2], Nawal Sarfraz [3], Maria Hayat [4], Rabia Bashir[2], Iqra Saif [2, 5], Anila Riasat[5], Tayyba Batool[2] and Bushra Aziz[6]

[1]Institute for Brain Sciences Research, Center for Translational Neuromedicine and Neurourology, School of Life Sciences, Kaifeng 475004, China
[2]University of Agriculture, Faisalabad, Pakistan
[3]Government College University Faisalabad, Pakistan
[4]Quaid e Azam University Islamabad, Pakistan
[5]Cholistan University of Veterinary and Animal Sciences, Bahawalpur, Pakistan
[6]Department of Zoology, Wildlife and Fisheries, Pir Mehr Ali Shah Arid Agriculture University, Rawalpindi, Pakistan
*Corresponding author: irumrana5545@gmail.com

Abstract

Progressive dopaminergic neuronal loss and peripheral neuronal degeneration are central to neurodegeneration. This is mechanistically linked to misfolded proteins and tauopathies. These harmful processes, often involving blood-brain barrier (BBB) disruption, underlie neurodegeneration in disorders such as dementia, Parkinson's disease, Alzheimer's disease, and traumatic brain injury. Such conditions pose significant challenges for diagnosis and treatment. Recent advancements in nanotechnology have facilitated the development of nanoparticles capable of crossing the BBB, enhancing drug delivery efficiency, and minimizing invasiveness. However, current animal models are inadequate in fully replicating human disease pathology, and nanomaterial synthesis remains complex. Advancements in nanomedicine are expected to address these challenges; it is poised to revolutionize neurodegeneration therapy.

Keywords: Nanoparticles, Bio imaging, Stem cell, Tauopathy, Genome editing, Drug delivery

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Introduction

Primary pathological aspects that contributing to neurodegeneration and cognitive decline include higher concentrations of α-syn in neuronal cells, fibrillary accumulation of amyloid β, and a hyperphosphorylated tau protein (Wu et al., 2024). These processes trigger progressive neural cells degradation, NDs are an extensive range of diseases that can result in motor, cognitive, and other neurological disorders. Kormas & Moutzouri (2023) identify ALS, HD, PD, and AD as examples of such prevalent diseases (Kormas & Moutzouri, 2023). Significant pathological and cellular mechanisms are commonly shared by various factors and demonstrating the possibility of collaboration and development of interconnected treatment strategies (Leng & Edison, 2021). These disorders influence millions of residents globally. Chronological age is a significant risk factor. However, genetic susceptibility and external variables such as lifestyle and environmental factors have an essential effect on the emergence and development of disease (Figure 1) (Liu et al., 2022).

Nanoscience examines the molecular and atomic structures of materials with characteristics at the nanoscale. By integrating this data into useful purposes, nanotechnology provides it accessible to generate cutting-edge technologies and procedures in an abundance of industries. Nanostructured materials, nanomaterials, nanoparticles, and nanocomposites are fundamental concepts (Lagashetty & Bhavikatti, 2019). Researchers from various scientific fields, including physics, predict that the application of nanoscale technologies and manufacturing approaches-ranging from robotics and nanomachines to nanomedicine and diagnostic tools, which will enable remarkable biomedical advancement (Erkoc & Ulucan-Karnak, 2021; Modi et al., 2021; Avula & Grodzinski, 2022; Talukdar et al., 2022).

The application of nano-biotechnology is rapidly advancing in the medical field to address a broad spectrum of medical problems, including disease detection, treatment, drug development, personalized medical approaches, cancer therapies, diagnostic methods, pharmaceutical developments, and novel techniques (Vaishampayan et al., 2023). Jennifer Doudna and Emmanuelle Charpentier were awarded the Nobel Prize in Chemistry for pioneering the CRISPR/Cas9 genome editing system (Ledford & Callaway, 2020).

Nano-based medicines and nano vaccines are gaining regulatory approval at an increasing rate, like traditional vaccines. In addition to advanced drug delivery systems such as polymeric nanoparticles and liposomes, various nanotechnology-based diagnostic devices, including nano-sensors and PCR assays are progressing. Commercialization of antibacterial drugs and nanomedicines, such as gene protocols and Doxil, is proceeding for both medical and scientific uses (Dessale et al., 2022). Recently, several kinds of nanoparticle developed including paramagnetic nanoparticles, nanocrystals, quantum dots, nanoshells, and nanosomes are utilized in medical purposes (Wang et al., 2021).

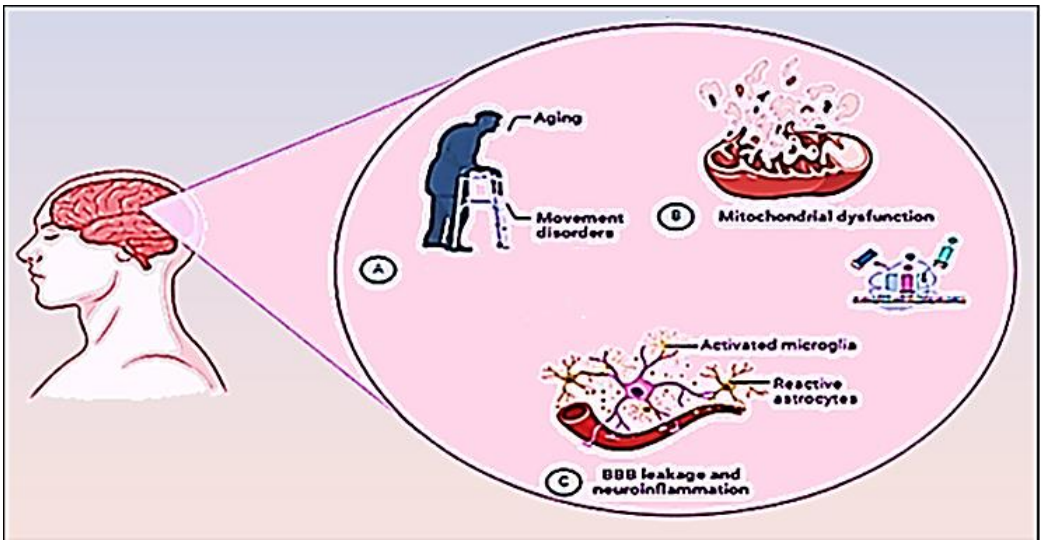

Fig. 1: Several risk factors involved in the progression of neurodegeneration

Structure, dimensions, charge, shape, and other physicochemical properties of nanocarriers significantly influence their safety and therapeutic efficacy. These factors affect toxicity, tissue penetration, and interactions with biological components. Because nanocarriers are more reactive than bulk materials, comprehensive risk assessments are necessary, accounting for their physicochemical properties across diverse biological systems (Domingues et al., 2022; Awashra & Młynarz, 2023).

Nanoparticles with nanoscale dimensions are effective in drug delivery due to surface modification, biocompatibility, PEGylation processes, and controlled drug release. Ahlawat et al. (2018) demonstrated their ability to prolong circulation, inhibit phagocytosis and cross the BBB (Ahlawat et al., 2018). Essential oils and green nanotechnologies (biopolymers) are advancing treatments for neurodegenerative disorders. Their novel usage involves drug delivery, brain regeneration, and biosensors (Cui et al., 2022; Monika et al., 2024).

Nanoparticles face challenges including low transfection efficiency, batch variability, limited drug loading, and accumulation. Polycationic carriers may trigger immune activation and lysosomal rupture, leading to oxidative stress, proteostasis disruption, mitochondrial dysfunction, and apoptosis (Wolfram et al., 2015).

1. Nano sized Drug Delivery Systems in Neurodegeneration

Compared to conventional medications, the use of nano-sized drug delivery systems offers superior electrical, mechanical, optical, and magnetic properties, making them highly advantageous for managing neurological disorders. Liposomes' low toxicity, low immunogenicity, high biocompatibility, and ability to cross the blood-brain barrier (BBB) make them highly valuable for neurological therapies. Intranasal delivery of nanoparticles containing mucoadhesive polymers extends their residence time in the nasal cavity, enhancing therapeutic efficacy. Polyphenols exert their antioxidant effects by activating cytoprotective proteins and NRF2-mediated pathways (Vieira & Gamarra, 2016; Yang et al., 2018).

Solid lipid nanoparticles are biodegradable lipid structures providing benefits such as enhanced absorption for poorly soluble drugs, decreased cytotoxicity, adequate biocompatibility, and resistance to drug degradation. Nanogels, characterized by their nanosized network structure and surface modifications, provide excellent retention rates and controlled drug release, helping to prevent drug degradation. Dendrimers, due to their highly branched and functionalized structure, serve as biocompatible carriers that enhance BBB permeability. Nano-emulsions, known for their ability to prevent premature drug release and interact effectively with serum proteins, improve drug solubility, bioavailability, stability, and CNS targeting (Naeimi et al., 2018; Scuto et al., 2021; Scuto et al., 2022).

Several applications require specifically designed engineering techniques. Currently, four key pathways for nanoparticles (NPs) to cross the BBB are being investigated. The first is passive diffusion, involving small hydrophobic molecules that can cross the BBB and enter the brain. The second is active transport via ABC transporters, which move molecules through endothelial cells by using ATP. Carrier-mediated transcytosis, the third transport mechanism, relies on endogenous cellular carriers to transport drugs. NPs can penetrate the blood-brain barrier (BBB) via four distinct mechanisms: ABC transporter activity, ligand-facilitated receptor-mediated endocytosis, carrier-mediated transcytosis, and passive diffusion of lipophilic molecules. Liposomal and polymeric nanocarriers are strategically used for organ-specific drug distribution, especially to hepatic and cardiac tissues, while inorganic NPs are critical to advanced ultrasound imaging through precise anatomical resolution with reduced cytotoxicity (Table 1) (Brown et al., 2020; Del Amo et al., 2021; Lomis et al., 2021; Sun et al., 2022).

2. Use of Nanoparticles Based Imaging Strategies in Neurological Disorders

Silver, gold, iron oxide, silica, and other inorganic nanoparticles (NPs) can penetrate the blood-brain barrier, reduce oxidative stress, and deliver diagnostic imaging agents (Rzigalinski et al., 2017; Dash et al., 2020; Kesharwani & Jain, 2022).

Nanowires and exosomes serve as advanced nanosystems for targeted drug delivery and controlled release kinetics. Quantum dots (QDs) are nanoscale semiconductors that exhibit size-dependent fluorescence, surpassing conventional imaging tools in sensitivity and multiplexing capacity (Figure 2). Their favorable bio interface properties and optical stability make them indispensable for biomedical applications such as molecular imaging, biosensing, and drug delivery (Villalva et al., 2021; Phafat & Bhattacharya, 2023).

Table 1: Categorization of nanoparticles based on their physicochemical properties, defined specifications, and application scopes with a focus on neuroprotection

Category	Sub-Category	Application	Reference
Carbon Nanoparticles	Graphene oxides, Carbon nanotubes, Fullerenes, carbon dots, Nanodiamonds	Facilitate drug delivery, Bioimaging, Blood glucose detection, Electric stimulation, Tissue reconstruction, Interaction with amyloid fiber, Antioxidants, Energy storage, Nanomedicine	(Park et al., 2019; Azimi et al., 2020; Ke et al., 2020; Xiang et al., 2023)
Organic Nanoparticles	Lipids, Nanocapsules, dendrimers, Protein based NPs, Micelles	Enhance drug efficacy, Control drug release, Drug toxicity reduction, Therapeutic agent, Self-healing system, Gene therapy, Biosensor	(Chen et al., 2020; Fonseca-Gomes et al., 2020; Kong et al., 2020)
Inorganic Nanoparticles	Metals, Metal oxides, Quantum dots, Bimetallic, Silica, Magnetic	Energy semi-conductor, Biosensor, Drug delivery, Magnetic applications, Chemical resistance, Environmental remediation, Solar cells	(Ke et al., 2020; Saghatchi et al., 2020; Mishra et al., 2021)
Exosomes	Based on cellular origin, Based on cargo types, Based on functional modifications, Artificial or mimetic exosomes, Based on disease-Specific applications	DNA cargo, Pathogenesis of diseases, Immune regulation, Biomarker, Drug delivery, Target cell-specificity enhancement,	(Aheget et al., 2020; Zhang et al., 2020; Kugeratski et al., 2021; Cummings et al., 2023)

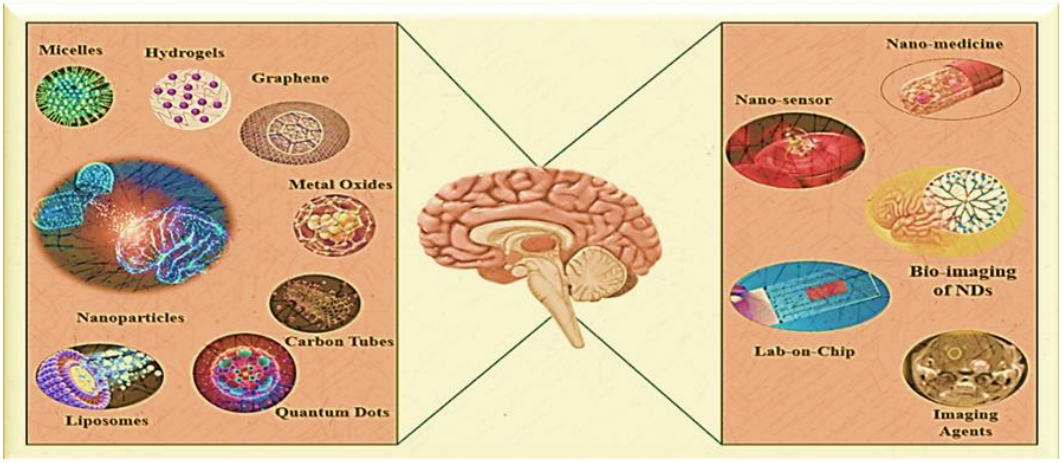

Fig. 2: Use of nanoparticle-based imaging applications in neurological disorders

3. Nanoparticle-Based Cell Targeting for Neurodegeneration and Reduction of Neuroinflammation

Greater expertise in neuroinflammation and CNS physiology is driving force behind the surface changes of NPs with ligands that boost cellular specificity and BBB penetration. These modifications, featuring CNS-targeted interventions, may improve the efficacy and safety of therapies for neurological diseases. (Chung et al., 2020; Hoyos-Ceballos et al., 2020; Juthani et al., 2020; Saha et al., 2020; You & Sabel, 2021; Landolina et al., 2022).

By eradicating cytotoxic agents, microglia provide a crucial role in protecting neurons. Chronic activation can lead to neurotoxicity by releasing inflammatory cytokines. Utilizing biocompatible, biodegradable materials with low immunological reactivity, taking advantage of microglial phagocytosis, and functionalizing NPs with receptor-specific ligands or peptides for targeted delivery are strategies needed for targeting microglia in neurological diseases. Additionally, incorporating co-delivered modulators that alter microglial activation and stop protein aggregation can improve the therapeutic stability and bioavailability of nanoparticles (Zhao et al., 2020).

4. Use of Nanotechnology in Protein Aggregation and Misfolding Cause Neurodegeneration

Nanotechnology has been employed in biomedical research to improve medication delivery, cerebral targeting, bioimaging, and stimuli-responsive chemotherapy for brain cancers. These advances are largely driven by the development of nanodrugs and nanocarriers. Molecular interventions in nanoparticle form demonstrate improved interaction with biological substrates and greater control over biochemical processes. The efficacy of anti-amyloidogenic small molecules can increase by up to 100,000-fold when formulated as colloidal nanoparticles. This advantage has been observed across a broad range of molecular therapeutics (Caballero & Gamez, 2021).

Tau dysfunction is central to Alzheimer's disease (AD) and more than 20 tauopathies, neurodegenerative disorders characterized by abnormal tau aggregation (Kovacs, 2018). These aggregates impair neuronal function, contributing to conditions such as AD and frontotemporal dementia (FTD). Despite growing interest in tau as a therapeutic target, no FDA-approved drugs exist, though clinical trials are ongoing (Cummings et al., 2023). Key therapeutic strategies aim to reduce tau hyperphosphorylation, enhance degradation, prevent aggregation, and improve cerebral blood flow (Cummings et al., 2023). NPs provide innovative approaches by enhancing drug delivery efficiency and interfering with tau aggregation mechanisms. Through advanced biochemical and mass spectrometry analysis, the discovery and development of next-generation therapeutics have identified to the identification of several significant phosphorylation sites associated with the advancement of disease (Figure 3) (Cummings et al., 2023).

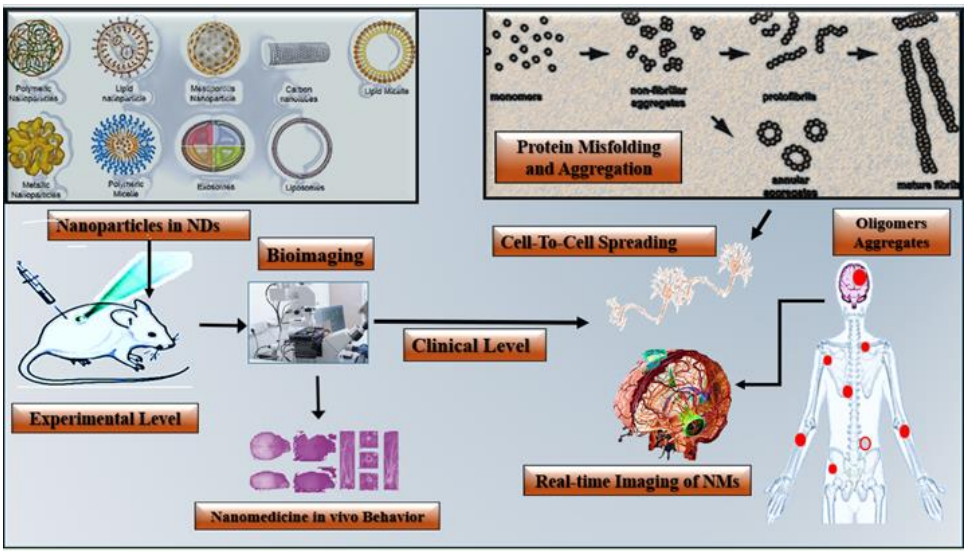

Fig. 3: Protein aggregation and role of nanoparticles at experimental and clinical levels

5. Nanocarriers for DNA, miRNA, and siRNA Delivery in Neurodegenerative Disease Models

The genes being targeted are effectively silenced by siRNA gene editing, which reduces the formation of phosphorylated Tau (p-Tau). However, due to both immune response and enzymatic degradation, nucleic acid therapies often exhibit low bioavailability. Although, nanocarriers inhibit these therapies prevent inactivation while in circulation. As a result, significant advancements have been made in the development of nanocarrier-based delivery systems for nucleic acid treatments in recent years (Aimo et al., 2022).

i. Gene Editing Technologies for Neuroprotection

Gene replacement, editing, and regulatory therapies for ophthalmology are advancing rapidly due to the neurodegeneration for gene therapy. Its small size reduces therapeutic dosages, while its accessibility facilitates precise delivery and real-time imaging. Moreover, genome editing minimizes systemic side effects. CRISPR-CasRx has shown potential for reducing choroidal neovascularization (CNV) and preventing vision loss in an AMD mouse model by specifically targeting the *Vegfa* gene. CRISPR-CasRx shows significant possibilities for the temporary silencing of damaging genes relevant to eye disease because of its superior specificity and efficacy. (Ong et al., 2019; Ziccardi et al., 2019).

Genome editing and therapeutic strategies employ zinc finger artificial transcription factors (ZFTFs), artificial transcription factors (ATFs), and antisense oligonucleotides (ASOs) for targeted gene regulation, as well as transcription activator-like effector nucleases (TALENs) for precise genome modifications. These genome editing tools enable critical processes such as gene disruption, modification, and regulation, positioning them as potential treatments for genetic disorders. Their broad applicability to target virtually any DNA-associated protein has made them a central focus of research and therapeutic exploration (Figure 4) (Fry et al., 2021).

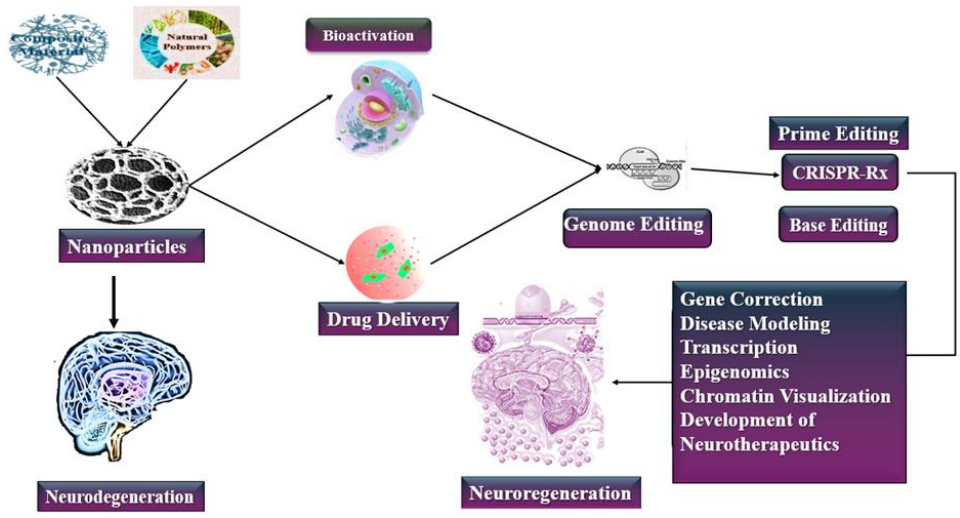

Fig. 4: Genome editing and its approaches in neurodegeneration

ii. Prime Editing Approach

Prime editing is a highly adaptable and precise genetic modification method, enabling the insertion of deletions, insertions, and all 12 nucleotide substitutions, along with their combinations. Although its application in neurodegeneration is promising, it remains in the early stages. This method facilitates the correction of mutations in genes such as CEG, SNCA, and LRRK2. It utilizes a Cas9 nickase (dCas9) combined with reverse transcriptase (RT) and is guided by a primary editing guide RNA (pegRNA). PE2, a Cas9 nickase-RT fusion, is more efficient than

PE1, its predecessor, specifically when using shorter primer binding sites. By introducing an additional guide RNA to target the non-edited DNA strand, PE3 and PE3b, advanced variants of the primary editing system, enhanced overall editing efficiency (Song et al., 2021; Jang et al., 2022).

iii. Site-specific Modifications in Neurodegeneration

Base editing is an advanced gene-editing approach that uses engineered base-editing enzymes fused to CRISPR-Cas9 proteins to directly convert one base in DNA or RNA to another without inducing double-stranded breaks (DSBs). This technique enables precise point mutations or corrections at specific genomic loci. Base editing enables CRISPR-Cas9-fused enzymes to target nucleotide substitutions and achieve precise point mutations in nucleic acids, reducing DSB-associated genomic instability and off-target changes common in homology-directed repair and non-homologous end joining (Suh et al., 2021).

6. Nanoscale Biomaterials for the Repair and Regeneration of Neural Tissue

To promote brain regeneration, researchers are advancing nanotechnology-based strategies to target both intracellular and extracellular pathological environments and to counteract injury-induced inhibitory mechanisms. This study underscores the significance of age-specific therapeutic strategies for an infant's brain. Despite advancements in regenerative medicine, spinal cord injury remains a significant challenge. Studies focus on the development of nanomaterials and their potential in SCI therapy. Furthermore, nanomaterials are highlighted for their ability to enhance emerging therapeutic strategies such as immunotherapy, CRISPR/Cas9, and optogenetic techniques (Cabeza et al., 2019).

Biomaterials are engineered to ensure integration with tissues and reduce adverse effects after implantation. Their broad application in the medical and diagnostic fields is primarily due to their low immunogenicity, remarkable biocompatibility, and regenerative potential. Chemical and modified surface scaffolding can control key cellular processes such as adhesion, proliferation, migration, and differentiation, supporting tissue healing both in vitro and in vivo. Synthetic biomaterials can be precisely designed for custom modifications in properties like stiffness, porosity, and biodegradability to suit specific needs. However, their biocompatibility can be influenced by the lack of recognition sites, necessitating chemical modifications to improve cell attachment and replicate the binding characteristics of native tissues (Ali & Bhuiyan, 2021; Li et al., 2021; Reddy et al., 2021; Xiang et al., 2023). Graphene-based nanomaterials (GBNs), PEG, chitosan, metal antibacterial agents, and CRL peptides are key components to the regeneration of SCI (Yari-Ilkhchi et al., 2024).

7. Stem Cell Therapy Using Nanomaterials in Neurodegenerative Diseases

The differentiation of stem cells is influenced by key physical properties of NPs, including the size, surface chemistry, morphology, and charge. Signaling pathways which facilitate differentiation can be stimulated mechanically by NPs. Neuronal differentiation has been observed to be improved via carbon-based NPs, including graphene, carbon nanotubes (CNTs), and C60 derivatives. It was previously and in the next illustration in figure 5 demonstrated that a water-soluble C60 derivative modified with alanine residues (Ala-C60) promotes neural stem cell (NSC) differentiation and proliferation while exhibiting resistance to oxidative stress. Moreover, in animal models, CNTs and NSCs together have demonstrated promise in regaining cognitive function and minimizing neurodegeneration. Due to their distinct optical, electrical, and magnetic characteristics especially when impacted by external electromagnetic fields metal NPs also aid in the regulation of stem cell fate (Lee et al., 2020; Hao et al., 2021; Hung et al., 2022; Ren et al., 2022).

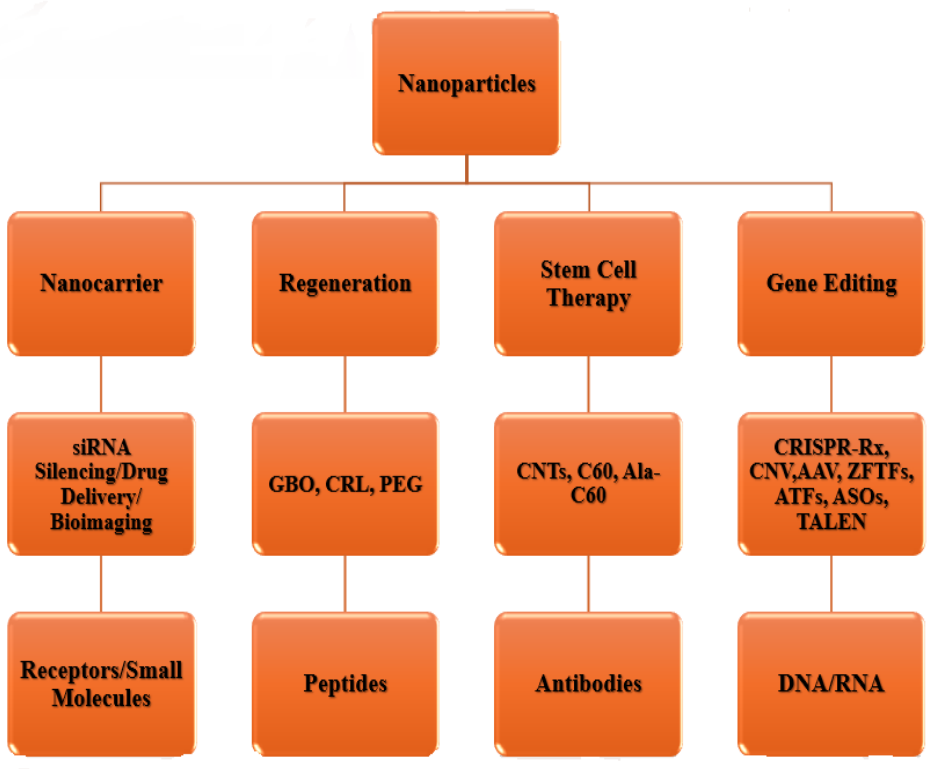

Fig. 5: Illustration of nanoparticle's mechanism in regeneration, stem cell therapy and bioimaging

8. Problems and Safety Issues with Nanotechnology in Neurodegenerative Medicine

Comprehensive nanotoxicology investigations have become significant as analysis on nanoparticle (NP) toxicity and its negative impacts on the environment and population remain in their early stages. Toxicity evaluation is important during the manufacturing of nano-therapies to deal with potential issues interlinked with their commercial and therapeutic applications (Abdul Basith Khan et al., 2020; Attarilar et al., 2020).

If nano-biomaterials break apart in the body's tissues, they could result in adverse effects because they are cytotoxic and have other detrimental effects. Clinical research highlights the composition of NPs has significantly influences cellular effects, including asbestosis. Carbon nanotubes (CNTs) have been linked with effects such as endosomal escape, chromosomal translocations, and plasma membrane permeability. Determining the cytotoxic processes become challenging by variability in surface chemistry, charge, and structure. CNTs based on graphene often include metal contaminants, are poorly soluble and biodegradability, and interact with other biomolecules, potentially disrupting genomic and proteomic processes in tissues and organs (Figure 6) (Augustine et al., 2020; Spurgeon et al., 2020).

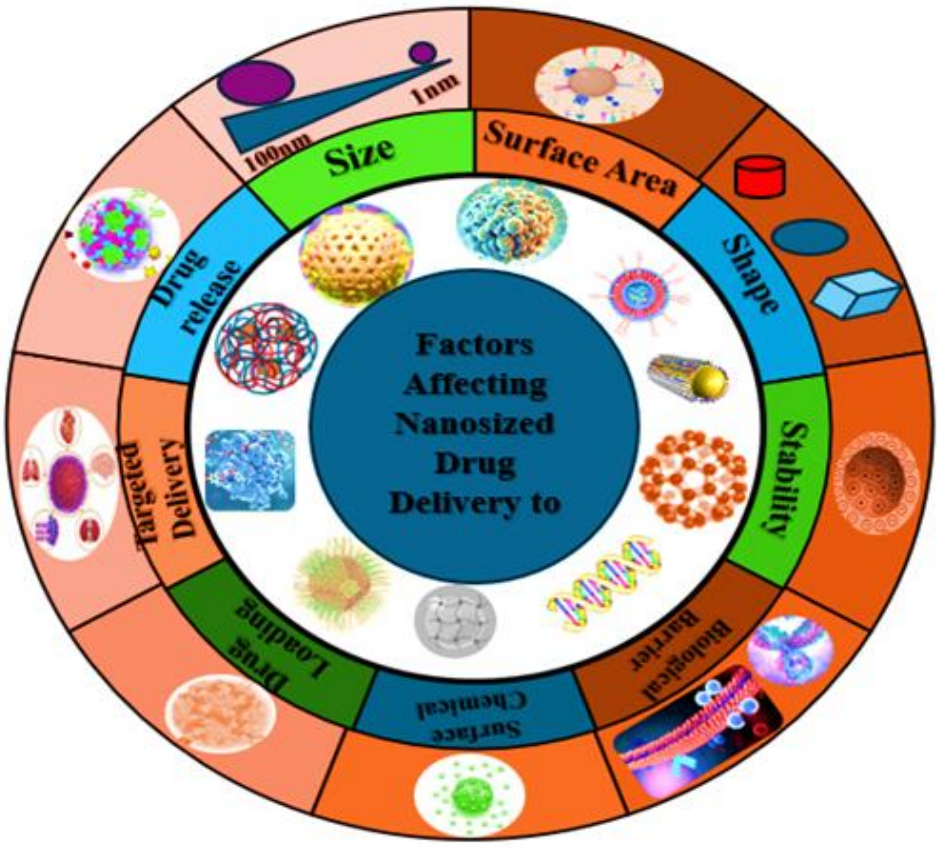

Fig. 6: Factors affecting nano-medicine drug delivery system to BBB

NPs can penetrate the sensory cells of the olfactory epithelium and migrate via the olfactory nerve to the olfactory bulb and cross the blood-brain barrier. Metallic NPs accumulate in the CNS and initiate a range of neurotoxic effects through oxidative stress, mitochondrial damage and DNA damage, inflammatory signaling, and cell death. The underlying mechanisms include ROS generation, apoptosis, cytokine release, microglial activation, and autophagy. The resulting dysfunction of both microglia and astrocytes exacerbates neurodegenerative outcomes in Alzheimer's and Parkinson's disease. MNPs@SiO_2 activate excitotoxicity via D-serine-mediated microglial signaling, AgNPs promote oxidative imbalance in the presence of Trolox, and AuNPs exhibit concentration-dependent cytotoxicity in neurons. CBNPs modulate inflammatory and apoptotic balance, while ZrO_2NPs are neurotoxic to the embryonic brain (Su et al., 2021).

9. Future Directions in Nanotechnology for Neurodegenerative Disorders

Nanotechnology offers bio-responsive biomaterials that have the potential to enhance the medical management of neurological disorders. These materials can adapt to patient-targeted needs and disease progression by monitoring CNS-specific signals and modulating drug delivery accordingly. Advanced imaging techniques combined with nanoparticles enable adaptive and precise therapeutic approaches by offering real-time feedback on treatment efficacy. Nano-biosensors further facilitate prompt detection and intervention by improving biomarker specificity and sensitivity. Additionally, nanotechnology aims to develop synthetic NPs that mimic the vital functions of natural tissues, reduce systemic toxicity, and optimize drug delivery methods.

Conclusion

The potential of therapies based on nanotechnology for neurological disorders is highlighted by developments in CNS-targeted medication

delivery. Although these nanoscale devices provide efficient brain-targeting techniques, they face challenges including a lack of models for assessing efficacy, material-specific limitations, immune activation, therapeutic agent degradation, and rapid clearance. Long-term efficacy and enhanced nanoparticle stability are necessary since gene therapies and nanoparticle treatments carry risks of off-target effects. Improved formulations, such as antibody-based NPs, can increase biomarker specificity. Interdisciplinary collaboration is crucial to overcoming these obstacles and developing nanotechnology for the treatment of neuronal diseases.

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