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NANOMEDICINE FOR NEURODEGENERATIVE DISEASES

PATIL M[*1], SHIMPI B[2], NIKAM Y[2], SHELKE R[2], SAINDANE T[2], HAKE S[2], CHATUR D[2], BORSE L[3] AND BORSE S[4]

1: Department of Pharmaceutics, Assistant Professor, Sandip Institute of Pharmaceutical Sciences, Nashik - 422213, Maharashtra, India

2: Department of Pharmaceutics, Research Scholar, Sandip Institute of Pharmaceutical Sciences, Nashik - 422213, Maharashtra, India

3: Department of Pharmacology, Professor and Principal, Sandip Institute of Pharmaceutical Sciences, Nashik - 422213, Maharashtra, India

4: Department of Pharmaceutical Chemistry, Associate Professor, School of Pharmaceutical Sciences, Sandip University, Nashik - 422213, Maharashtra, India

***Corresponding Author: Ms. Mayuri Patil: E Mail: mayuripatil150597@gmail.com; mayuri.patil@sandippharmacy.org**

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ABSTRACT

Neurodegenerative diseases pose a growing global health crisis, with no curative treatments currently available due to the formidable blood-brain barrier limiting drug delivery. Nanomedicine offers innovative solutions by utilizing Nano carriers like nanoparticles, liposomes, and polymeric micelles to encapsulate therapeutics and enable brain targeting. This review systematically examines emerging Nano carrier platforms for enhanced diagnosis and therapy of neurodegenerative disorders. Lipid-based, polymeric, inorganic, and biomimetic Nano carriers are discussed, highlighting their unique advantages in crossing the blood-brain barrier, targeted delivery, sustained release, multimodal imaging, and neuroprotection. Novel brain penetration strategies like inhibiting efflux transporters, polymer conjugation, and active targeting ligands are explored. Applications in early detection, neural regeneration, and combination therapies are presented. While challenges persist, the review provides insights into potential breakthroughs leveraging biomimetic design, advanced targeting, gene editing, and

theranostic integration. Overall, nanomedicine represents a promising paradigm to revolutionize neurodegenerative disease treatment.

Keywords: Alzheimer's disease, Huntington's disease, nanomedicine, nanoparticles, nanotechnology, and Parkinson's disease

INTRODUCTION:

The global prevalence of neurodegenerative diseases, such as Alzheimer's and Parkinson's, is increasing as populations continue to age. These diseases cause progressive nerve cell damage and death in the brain, leading to problems with movement and memory that severely reduce quality of life. Neurodegenerative diseases are conditions where nerve cells in the brain gradually degenerate and die, causing difficulties like ataxia (trouble moving) or dementia (memory and thinking issues). Symptoms worsen over time, sadly leading to death. Alzheimer's is the most prevalent neurodegenerative disease, causing over 50% of dementia cases in America. Others like Parkinson's, Huntington's, and ALS are also quite prevalent. Despite much research, there is still no cure, and patients experience slow decline. Current treatments only manage symptoms and don't halt disease progression. Finding a treatment that slows neurodegeneration would greatly help patient's live better longer[1]. A major challenge is getting drugs across the blood-brain barrier into the brain. The blood-brain barrier protects the brain by blocking entry of cells and particles from blood but also obstructs most drugs from reaching the brain even after intravenous injection. Less than 1% of an injected drug enters the brain, if at all. Thus, the high systemic doses needed for therapeutic brain levels can be toxic for the body[2]. Better techniques are needed to safely deliver therapies into the central nervous system[3].

Nanomedicine offers innovative therapeutic approaches to cross the restrictive blood-brain barrier and directly target neurodegeneration pathways. Nanoparticles, liposomes, micelles, dendrimers, Nano gels, nanoemulsions, and other Nano carriers can encapsulate and protect small molecule drugs and biologics like antibodies, proteins, peptides, siRNA, mRNA, and plasmid DNA. This enhances their stability and circulation time in the bloodstream[4, 5]. Nano carrier surfaces can be functionalized with targeting moieties like antibodies, aptamers, peptides, or small molecules to enable preferential accumulation and cellular uptake in the brain versus peripheral organs[6]. This allows localized delivery of therapeutics while avoiding systemic toxicity. The high surface area-to-volume ratio of Nano carriers also facilitates the delivery of enzymes, antioxidants, neurotropic factors, and other

agents to modulate cell signalling and molecular pathways driving neuroinflammation, protein misfolding, and apoptotic cell death[7].

The primary goal is to develop effective interventions that positively impact the rhythm and progression of human CNS disease. Achieving these goals is thought to require specialized knowledge across multiple fields, including biomedical sciences (neuroscience, pathology, immunology, pharmacology, and molecular imaging) as well as material, biomaterial, and pharmaceutical sciences (polymers, nanomaterial's, drug delivery, and gene delivery). Although numerous comprehensive reviews on brain drug delivery have been published in recent years [8, 9], none have focused on the most recent and impactful studies involving cell- and polymer-based nanomaterial's for CNS delivery. In this regard, modified discussions are presented to outline disease processes and requirements in conjunction with current research efforts in nanomedicine. This work was conducted with the aim of improving the diagnosis and treatment of neurodegenerative disorders. The review is organized into several key sections [10, 11]. First, it provides an overview of these disorders, including the role of bio imaging in disease diagnosis. Second, it addresses the challenges that must be overcome to achieve effective treatment for CNS diseases. Third, it outlines the main types of Nano carriers (such as liposomes, nanoparticles, polymeric micelles, Nano gels, and others) that show potential for delivering diagnostic and therapeutic agents to the brain[12]. Fourth, it discusses cell-mediated delivery of Nano carriers to targeted brain areas and their potential to improve pharmacokinetics in the body. Fifth, it explores the use of polymeric inhibitors to block drug efflux systems, thereby selectively increasing the permeability of therapeutic agents across the blood-brain barrier. Finally, it examines chemical modifications of proteins, particularly conjugation with amphiphillic block copolymers, as innovative strategies to enhance protein delivery to the brain[13].

Neurodegenerative diseases:

Neurodegenerative diseases are a group of disorders marked by the gradual deterioration of the nervous system. These conditions result in the gradual dysfunction and loss of neurons, leading to various cognitive, motor, and sensory impairments. The pathophysiology of neurodegenerative diseases is complex and involves a combination of genetic, environmental, and age-related factors.

Common neurodegenerative diseases are as follows:

1. Alzheimer's disease
2. Parkinson's disease
3. Huntington's disease

4. Amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease)
5. Multiple sclerosis (MS)
6. Frontotemporal dementia
7. Progressive supranuclear palsy (PSP)
8. Corticobasal degeneration (CBD)
9. Creutzfeldt-Jakob disease (CJD)
10. Spinocerebellar ataxia
11. Wilson's disease
12. Charcot-Marie-Tooth disease
13. Spinal muscular atrophy (SMA)
14. Friedreich's ataxia
15. Lewy body dementia

Alzheimer's disease:

Alzheimer's disease (AD) is a devastating condition characterized by the progressive deterioration of the brain, which occurs as a result of the formation of plaques in the hippocampus[14]. The formation of these plaques begins approximately 20 years before the appearance of clinical symptoms, making it challenging to fully understand the precise pathological progression of AD[15]. The global prevalence of AD is increasing, with over 50 million individuals affected in 2019, leading to a significant economic and workforce burden. According to projections, AD may affect 13.8 million Americans 65 and older by the middle of the twenty-first century, ranking it as the sixth most common cause of death in the country[16].

The most significant risk factors for Alzheimer's disease include advanced age (usually over 65 years, though this is not a strict definition) and the presence of at least one APOE ε4 allele[17]. Additionally, women are more likely than men to develop Alzheimer's, especially after the age of 80[18]. Despite having a similar amyloid β burden, women also tend to have a higher tau burden[19]. In addition, cardiovascular risk factors and poor lifestyle choices have been associated with a higher risk of dementia. The Lancet Commission on Dementia Prevention states that these 12 modifiable risk factors together account for around 40% of the global risk for all types of dementia[20].

Parkinson's disease:

Parkinson's disease (PD), first described by James Parkinson in 1817, is a debilitating neurodegenerative disorder with no cure. It affects 1-2% of individuals over the age of 50, with approximately 1.5 million cases in the United States alone. The disease is characterized by the progressive loss of dopaminergic neurons containing neuromelanin in the substantia nigra pars compacta (SNpc), as well as the accumulation of eosinophilic, intracytoplasmic protein inclusions known as Lewy bodies (LB) and dystrophic Lewy neurites in the remaining neurons. While the loss of neurons in the SNpc is a prominent feature, the disease also causes widespread neurodegeneration throughout the central

nervous system (CNS), with the pars compacta being affected in the intermediate stages of the condition[21, 22].

Around 70% of Parkinson's disease patients experience the characteristic tremor, while many others exhibit more subtle symptoms. These can include sensations of numbness or pain without clear sensory loss. Patients often report muscle pain and tenderness, along with weakness or stiffness in their limbs. Difficulty with tasks such as handwriting, performing repetitive actions like brushing teeth, winding a watch, buttoning clothes, or using utensils is a common issue for several months. Fatigue, depression, and a general sense that time is moving slowly and life feels monotonous are also frequent complaints [23, 24].

Huntington's disease:

George Huntington was the first to address and depict the disease, which is now known as Huntington's chorea. This neurodegenerative disorder is inherited within families from one generation to the next, typically manifesting in middle age with symptoms including involuntary choreatic movements, behavioral and psychiatric disturbances, and dementia[25]**.** The disease was originally referred to as Huntington's chorea until the 1980s, when the name was changed to Huntington's disease (HD) to reflect the broader non-motor symptoms and signs associated with it. In 1983, a linkage on chromosome 4 was established, and in 1993, the gene responsible for HD was identified. This period saw a notable surge in interest in Huntington's disease (HD) and other neurogenetic disorders. For the first time, premanifest testing became a reality, and as more diseases linked to CAG trinucleotide repeats were identified, HD emerged as a model for many medical studies. CAG refers to a trinucleotide sequence consisting of cytosine (C), adenine (A), and guanine (G), which serves as the building block of DNA and codes for the amino acid glutamic[26]

Amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease):

Amyotrophic lateral sclerosis (ALS) is a specific type of motor neuron disease that exhibits both upper and lower motor neuron symptoms. The term "amyotrophic" refers to the muscle wasting, weakness, and twitching that result from damage to the lower motor neurons. "Lateral sclerosis" describes the hardness found in the spinal cord's lateral columns upon post-mortem examination, where gliosis occurs after the degeneration of the corticospinal tracts. The clinical features of ALS include upper motor neuron signs such as hyperactive tendon reflexes, Hoffmann signs, clonus, and Babinski signs. ALS has two meanings: it refers to several adult-onset conditions involving the progressive degeneration of motor neurons, and in the United Kingdom, it is referred to as “motor neuron disease”[27].

Multiple sclerosis (MS):

Multiple sclerosis (MS) is a chronic inflammatory disorder that impacts the central nervous system. As an autoimmune disease, MS is the leading cause of non-traumatic neurological disability in young adults. Diagnosing MS involves identifying lesions that are both spatially and temporally distinct while ruling out other inflammatory, infectious, or genetic conditions with similar clinical symptoms. The disease manifests in three primary forms: relapsing-remitting MS, which involves episodes of neurological dysfunction followed by periods of stability; primary-progressive MS, where progressive neurological disability begins at the onset; and secondary-progressive MS, where progressive disability develops later in the disease's progression[28].

Frontotemporal dementia:

Frontotemporal dementia is a neurodegenerative clinical disorder characterized by progressive deficits in behaviour, executive function, and language[29, 30]**.** Frontotemporal dementia is a diverse group of non-Alzheimer dementias that collectively involve distinct and progressive degeneration of the frontal or temporal lobes, or both. The earliest descriptions of frontotemporal dementia cases date back to the late 19th century, primarily by Arnold Pick, who initially referred to the condition as Pick's disease. However, it has only been in the last 30 years that the clinical and pathological complexity of these diseases and their recognition as distinct forms of brain degeneration have been fully understood. Frontotemporal dementia is rarer than Alzheimer's disease, with prevalence estimates ranging from four to 15 per 100,000 people under the age of 65, according to studies in Europe and the US. Despite its lower prevalence, this group of diseases remains a significant cause of early-onset dementia, with substantial financial and human impacts[31].

Progressive supranuclear palsy (PSP):

Progressive supranuclear palsy (PSP) is a unique type of Parkinsonian disorder marked by progressive stiffness in the trunk, difficulty with vertical eye movements, speech difficulties (dysarthria), and swallowing problems (dysphagia). It was first identified by Steele, Richardson, and Olszewski in 1964[32]. This condition manifests with a range of symptoms affecting balance, vision, speech, movement, and swallowing. These symptoms may include difficulties with walking balance, eye movement coordination, light sensitivity, speech articulation, swallowing function, behavioral changes, memory impairment, sleep disturbances, light sensitivity, and mood disturbances[33]**.** Additionally, frontal lobe dysfunction and subcortical dementia

can sometimes be observed. PSP typically presents in late middle age with features such as bradykinesia and rigidity similar to Parkinson's disease (PD), but distinguishes itself through severe gait disturbances, supranuclear gaze palsy, and early pseudo bulbar signs[34, 35]. Other key characteristics of PSP include dementia, emotional liability, axial extensor dystonia, poor response to levodopa treatment, and a more rapid disease progression compared to untreated PD. In some atypical cases, patients may exhibit apraxia of speech, corticobasal syndrome, or spastic paraparesis[36].

Corticobasal degeneration:

Corticobasal degeneration is an uncommon, progressive neurodegenerative disorder marked by unique motor symptoms and a range of clinical presentations that may also occur in other conditions[37, 38]. The clinical variability and lack of specificity of CBD present a significant diagnostic challenge even to movement disorder specialists[37, 39]. It shares tau-related pathology with other conditions, including Alzheimer's disease (AD), Pick's disease, and progressive supranuclear palsy (PSP), particularly the presence of four-repeat (4R tau) isoforms. This common tau pathology may explain the overlapping clinical features observed among these disorders. The classic clinical description of corticobasal degeneration, specifically corticobasal syndrome (CBS), was initially outlined by Rebeiz and colleagues in 1967[40].

Creutzfeldt-Jakob disease (CJD):

Creutzfeldt-Jakob disease, also known as transmissible spongiform encephalopathy, is a group of lethal neurodegenerative disorders that impact both humans and animals. This rare and rapidly progressive disorder is characterized by the degeneration of the brain and is classified into sporadic, genetic, and acquired forms. Although the term "sporadic" is commonly used to describe this disease, it could be argued that "idiopathic" is a more appropriate term, as the exact cause of this form of CJD remains unknown despite its consistent occurrence worldwide, with an estimated frequency of approximately 1 case per million individuals annually[41, 42].

Spinocerebellar ataxias (SCA):

Spinocerebellar ataxias (SCA) are a collection of inherited cerebellar ataxias that are transmitted through an autosomal dominant pattern. These disorders are characterized by progressive neurodegeneration, specifically the degeneration of the cerebellum and potentially other interconnected regions such as the brain stem. [43] Ataxia refers to a clinical condition of incoordination, denoting a lack of order. Moreover, the term ataxia is also used to refer to a specific group of degenerative nervous system diseases where progressive ataxia is the primary

clinical symptom. Ataxias can have both genetic and non-genetic causes, with spinocerebellar ataxias (SCAs) being the genetically inherited, autosomal dominant forms among them**.** [44, 45]**.**

Wilson's disease:

Wilson's disease is an uncommon autosomal recessive genetic condition that impairs the body's ability to metabolize copper. It is characterized by both hepatic and neurological symptoms. The prevalence of this disease is estimated to be between one in 30,000 and one in 100,000 individuals. The disorder was first identified by Kinnier Wilson in 1912[46]. Over the past two decades, significant advancements have been made in our understanding of the disease's pathogenesis, cellular biology, and molecular genetics. The majority of symptoms typically manifest during the second and third decades of life. In individuals with Wilson's disease, there is an accumulation of excess copper in the liver due to impaired copper excretion in bile. The concerning aspect of this condition is its progressive nature, potential for remaining undiagnosed, and the possibility of being fatal if left untreated. In the early stages of the disease, copper build up can only be identified using specialized immune histochemical stains, which are not commonly accessible. This early copper accumulation is associated with macrosteatosis, microsteatosis, and glycogenated cores, which are also observed in other disorders such as non-alcoholic steatohepatitis.

Charcot-Marie-Tooth disease:

Charcot-Marie-Tooth (CMT) disease, also referred to as hereditary motor and sensory neuropathy (HMSN), includes a range of disorders that vary both clinically and genetically. These conditions are marked by muscle atrophy, weakness, and sensory impairment, with the most pronounced symptoms usually affecting the distal parts of the body. The disease was first described in 1886 and was named after the three clinicians who initially reported it. It is the most common inherited neuromuscular disorder, affecting at least 1 in 2,500 individuals**.**[48]**.** The understanding of CMT has evolved over time, with two distinct periods of advancement. The first period, from 1886 to 1991, was the pre-genetic era. During this time, there were significant advancements in the understanding of peripheral nerve diseases in general. From the perspective of CMT, this period was particularly important for the development of techniques to study peripheral nerve neurophysiology and pathology**.**[49,50].

Spinal muscular atrophy (SMA):

Spinal muscular atrophy (SMA) refers to a group of inherited conditions characterized by the degeneration of motor neurons in the spinal cord, leading to muscle wasting and weakness. SMA is a serious neuromuscular

disorder marked by the progressive weakening and paralysis of proximal muscles due to the degeneration of alpha motor neurons. The disease was first described in the 1890s by Werdnig and Hoffmann. In 1995, the discovery of the survival motor neuron (SMN) gene confirmed it as the genetic cause of SMA [51, 52].

Friedreich's ataxia:

Between 1863 and 1877, Nicholaus Friedreich published five papers that described a disease now known as Friedreich ataxia (FRDA). In these reports, Friedreich detailed the characteristics of the condition, which he named after himself, based on observations of nine individuals from three families. His initial findings highlighted that the onset of symptoms typically occurred during childhood, and manifestations such as ataxia, dysarthria, sensory loss, muscle weakness, scoliosis, foot deformities, and cardiac symptoms were present. However, it was not until the last two reports[53] that the debate regarding the diagnosis of FRDA arose. Some researchers argued that the absence of knee and ankle reflexes could rule out the diagnosis, while others disagreed. Early publications on the subject were further complicated by the inclusion of cases that are now recognized as not being FRDA. Furthermore, the occurrence of spastic paraparesis, a condition similar to FRDA, has led to some confusion. Bell and Charmichael proposed that spastic ataxia might be a subset of FRDA, a view that Harding disagreed with. It is important to highlight that FRDA is the most common inherited form of ataxia.[54]

Lewy body dementia:

Dementia with Lewy bodies is a common form of dementia, with about 80% of people with Parkinson's disease eventually developing dementia. Although these two conditions differ in the timing of dementia onset and parkinsonism, both diseases share similar motor and cognitive changes as they progress, indicating that they may represent a continuum rather than separate disorders. Together, they are known as Lewy body dementias. This review highlights developments following a key 2004 analysis and the subsequent dementia with Lewy bodies consortium criteria. While the consortium criteria show high specificity when core and suggestive features are present, their sensitivity is only moderate. Accurate diagnosis is essential for effective management, as these patients require a personalized treatment approach. Ongoing clinicopathological research in both dementia with Lewy bodies and Parkinson's disease dementia has led to considerable advancements. [55].

Nanomedicine:

Nanomedicine involves the application of nanotechnology in healthcare, using Nano

scale materials and devices for diagnostic, therapeutic, and preventive purposes. Many diseases arise from changes in biological structures at the atomic or Nano scale level. Mutations in genes, misfolded proteins, and infections caused by viruses or bacteria can disrupt cellular function or communication, sometimes resulting in life-threatening conditions. These particles and pathogens are on the Nano scale and exist within biological systems that are protected by nanometre-sized barriers, like molecular pores approximately 9 nm wide. Their chemical properties, size, and shape influence how molecules are transported to specific biological areas and how they interact. Nanotechnology is the intentional design, characterization, production, and use of materials, structures, devices, and systems by manipulating their size and shape within the Nano scale range (1 to 100 nm). Because nanomaterial's share a similar scale to biological molecules and systems but can be engineered for various functions, nanotechnology offers significant potential for medical applications. [56]. Nanoparticles like liposomes and dendrimers can be modified with ligands such as transferrin receptor antibodies or lactoferrin that target receptors on the BBB, facilitating active transport through receptor-mediated transcytosis. Nanoparticles made from polymers like PLGA allow for the adjustment of drug release from days to months based on polymer composition, enabling sustained drug release for prolonged therapeutic effects. Inorganic nanoparticles like iron oxide and gold nanoparticles possess inherent imaging properties or can be linked to contrast agents like gadolinium, making them suitable for diagnosis and imaging of neuroinflammation.[57]

Nanomedicine offers innovative approaches to enhance the safety and effectiveness of traditional therapeutics. By targeting drugs with lower bioavailability to specific locations, nanomedicine can reduce the required dosage. The larger surface area and increased reactivity of nanoparticles may reduce the required drug dosage, thereby improving toxicity profiles and enhancing patient compliance. Moreover, the extensive surface area of nanoparticles can increase drug dissolution rates, saturation solubility, and cellular uptake, leading to improve in vivo performance. Through the combination of encapsulation, controlled release mechanisms, and surface modifications, nanomedicine can significantly improve therapeutic targeting and bioavailability, making it several times more effective than traditional treatments. Targeted nanoparticles can also deliver a higher dose.[58]

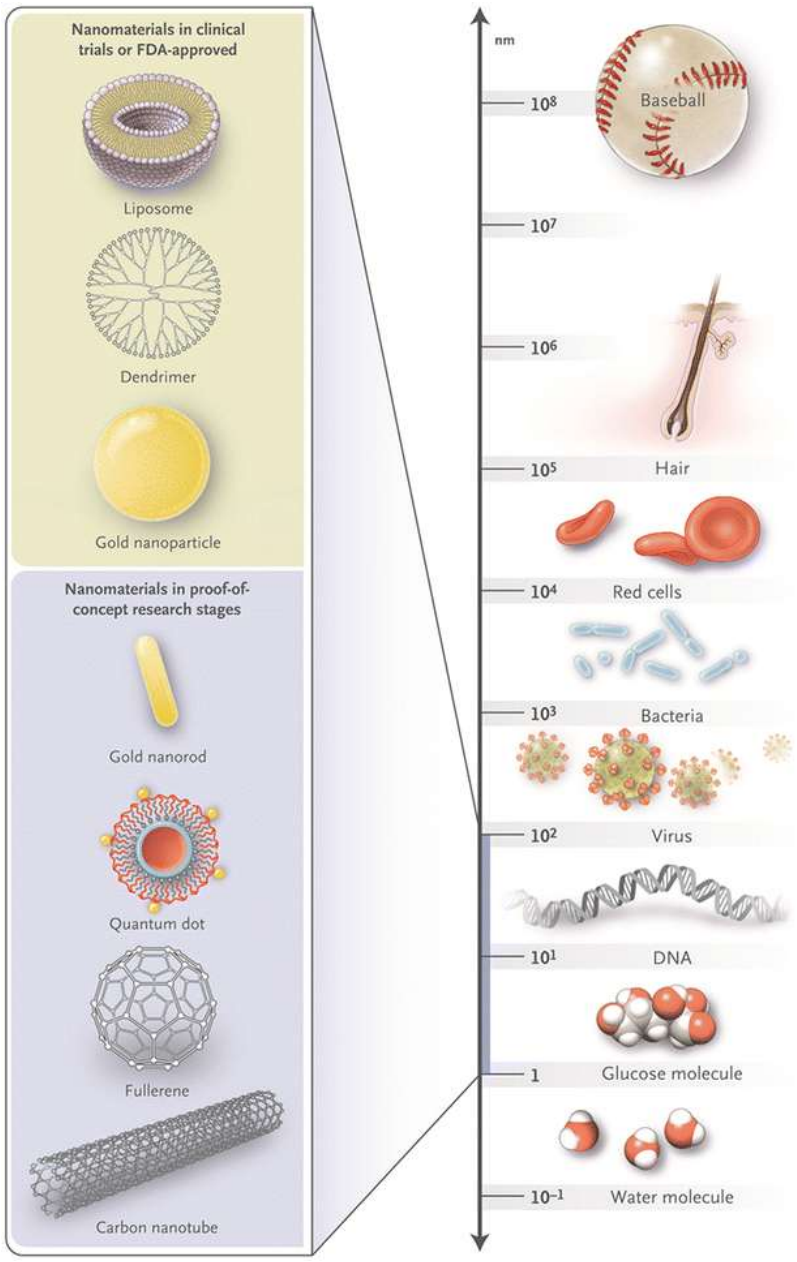

Figure 1: Examples of the nanomaterial's most commonly used in medicine [59]

Ongoing research is focused on developing advanced nanoparticles (NPs) for the targeted delivery of various therapeutic or diagnostic agents. The appeal of targeted NP applications arises from the ability to use MRI to track the particles and correlate the results with histological observations following treatment. Polymer/SPIO composites are the most widely used NPs for theranostics (diagnostics). In addition, multiple cancer drugs can be attached to a polymer/IO conjugate backbone, allowing for their release at the tumour site where they can work together synergistically, potentially enhancing effectiveness. Furthermore, electromagnetic fields can be

applied remotely to generate heat in SPIO NPs, enabling thermal ablation therapy, as SPIO NPs produce heat when exposed to an alternating field.

Nanotechnologies have already transformed genetic and biological analysis through devices that assess molecular biomarkers. Unlike traditional methods, these tests are faster, more reliable, and cost-effective, thanks to in vitro and in vivo diagnostic innovations that use nanochips or quantum dots (QDs). Nanotechnology can also create diagnostic tools that are more sensitive, allowing for the early detection of metabolic imbalances, which could help prevent diseases like diabetes and obesity. The ongoing use of nanotechnologies to develop better and more affordable methods for identifying molecular biomarkers will also facilitate the widespread use of personalized medicine.

Nanomedicine for Neurodegenerative Disease:

Neurodegeneration is the term used to describe the gradual loss of a neuron's structure and function, which eventually results in its death. This process gives rise to a wide range of debilitating disorders of the central nervous system (CNS), collectively known as neurodegenerative disorders (NDs). Neurodegenerative diseases (NDs) include conditions such as Alzheimer's disease (AD), Parkinson's disease (PD), prion diseases, amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD). Neurodegeneration can take place at different levels within the neuronal environment, ranging from the molecular to the systemic level. Extensive global research has revealed several subcellular and molecular similarities among these NDs, such as abnormal synaptic activity and the accumulation of misfolded proteins in the brain, which may provide insights into the development of effective therapeutic approaches. In contrast, other brain-related illnesses like stroke or cancer exhibit distinct subcellular differences. [62]

Various factors contribute to the onset and progression of neurodegenerative diseases (NDs), including genetic mutations, protein misfolding and aggregation, mitochondrial dysfunction, DNA damage, damage to organelle membranes, apoptotic or autophagic cell death, and transglutaminase binding. Aging is considered a significant risk factor for most NDs, as they typically appear later in life, likely due to alterations in mitochondrial DNA and increased oxidative stress.

The main treatments for managing motor symptoms include levodopa (often combined with a dopa decarboxylase inhibitor and, in some cases, a catechol-O-methyltransferase (COMT) inhibitor), dopamine agonists, and monoamine oxidase-B (MOA-B) inhibitors. Huntington's disease, another genetically

inherited and debilitating condition with no cure, affects 5–15 out of 100,000 individuals globally. The most effective drug for managing cognitive symptoms is Tetrabenazine, followed by neuroleptics and benzodiazepines. Currently, amyotrophic lateral sclerosis (ALS) is the most severe motor neuron disease and remains without a cure. Although its mechanism is not fully understood, Riluzole and Edaravone are the most widely used treatments for ALS.

Prion disease has led to some of the most unexpected discoveries, where a protein functions as an infectious agent and causes neurodegeneration. Researchers are actively working to identify new drugs to treat this rare but fatal condition. As a result, finding novel therapeutic strategies for managing and potentially eliminating neurodegenerative diseases is essential. However, the primary challenge in developing effective treatments is the limited ability of therapeutics to cross the blood-brain barrier (BBB).

Nanotechnology, despite its well-demonstrated influence, is currently being extensively researched to discover potential solutions for Neurological Disorders (NDs). When appropriately manipulated, nanomaterials with specific physico-chemical properties such as structure, polarity, size, charge, surface chemistry, etc., have the capability to penetrate the blood-brain barrier (BBB) and target the central nervous system (CNS) to deliver therapeutic cargo. This review will explore recent developments in different types of nanoparticles (NPs), such as liposomes, polymeric nanoparticles, metal nanoparticles, and bio-nanoparticles, for the treatment and diagnosis of various neurodegenerative diseases (NDs). It will also address topics like neuroprotection, neuronal tissue regeneration, clinical progress, safety, toxicity, and the challenges associated with using nanomedicine in NDs. Finally, the future prospects of Nano technological approaches in addressing NDs will be discussed in detail.[63]

Types of Nanomedicine in Neurodegenerative Diseases for Treatment

- Lipid-Based Nanoparticles
- Solid lipid nanoparticles (SLN)
- Nanostructured lipid carriers (NLC)
- Polymeric Nanoparticles
- For diagnostic purposes
- Inorganic Nano carriers
- Iron oxide nanoparticles
- Gold nanoparticles
- Quantum dots
- Radiolabeled nanoparticles
- Plasmonic gold nanoparticles

ADVANTAGES OF NANOMEDICINES

Crossing the blood-brain barrier: Nanoparticles can be modified with targeting ligands to penetrate the challenging blood-brain barrier and deliver

drugs directly to the brain. This enhances the delivery of drugs that typically suffer from low bioavailability.[64]

- **Drug protection:**
    - Nano carriers allow encapsulation of drugs and protect them from degradation as well as premature clearance. This increases half-life and circulation time.[65]
- **Sustained release:**
    - Nanomedicine from polymers, lipids, etc., provide controlled and sustained release of drugs over long periods. This improves efficacy and reduces dosing frequency.[66]
- **Solubility enhancement:** Poorly water-soluble drugs like curcumin can be incorporated into Nano carriers like liposomes to enhance solubility. This improves bioavailability.[67]

Targeted delivery: Active targeting ligands enable Nanomedicine to selectively deliver drugs to affected areas and cells in the brain. This reduces off-target effects.[68]

Combination therapy: Nano carriers can co-deliver multiple therapeutic agents and genes for synergistic effects. This overcomes limitations of monotherapy.[69]

Lesser side effects: Nanomedicine accumulate less in normal tissues, thereby reducing systemic side effects associated with high doses of traditional drugs.[64]

Diagnosis and imaging: Nanoparticles can incorporate imaging agents and enable diagnosis of neurodegeneration along with therapy.

Patient compliance: Reduced dosing frequency improves patient compliance to medication regimes, especially in chronic neurodegenerative disorders.[66.]

Nanomedicine Strategies in Neurodegenerative Disorders

A. Drug Delivery

1. Nanoparticle-based drug delivery systems

Polymeric nanoparticles made from FDA-approved biodegradable polymers like PLGA (poly (lactic-co-glycolic acid)) and chitosan have been widely explored for sustained and controlled drug delivery. PLGA nanoparticles can encapsulate hydrophobic small molecule drugs and hydrophilic macromolecules like proteins and peptides using techniques like emulsion solvent evaporation and Nano precipitation. To prevent systemic toxicity, PLGA is hydrolysed in the body to produce the metabolite monomers lactic acid and glycolic acid. The lactide/glycolide ratio and molecular weight of PLGA nanoparticles determine how quickly drugs are released from them. For example, tacrine-loaded

PLGA nanoparticles provided sustained drug release over 120 hours in vitro and residence in the brain for up to 15 days after intranasal administration in an Alzheimer's disease rat model.[70] Chitosan is a biocompatible cationic polymer that can form nanoparticles through ionic gelation with polyanions like triphosphate. Chitosan nanoparticles have shown enhanced cargo encapsulation efficiency owing to strong electrostatic interactions.

Intranasal delivery of curcumin using chitosan nanoparticles functionalized with rabies virus glycoprotein showed 5-fold higher drug levels in the brain compared to intravenous delivery in a mouse model.[72] Triglycerides, fatty acids, and other biocompatible and biodegradable lipids make up lipid-based nanoparticles, such as solid lipid nanoparticles (SLN), which stay solid at normal temperature. SLNs are suitable for the encapsulation of highly lipophilic molecules like alpha-mangostin, which showed 85% entrapment efficiency and sustained release across 96 hours.[73] Nanostructured lipid carriers (NLC) are an improved generation of SLN, with controlled nanostructures for optimal drug loading. Clioquinol-loaded NLC administered intravenously led to 3.6-fold higher drug accumulation in the brain compared to free drug.[74]

2. Targeted drug delivery to the brain:

Transport of chemicals into the brain is carefully regulated by the blood-brain barrier (BBB), which is made up of tight connections between endothelial cells. Nonetheless, the BBB's receptors can be used to deliver nanoparticles to the brain precisely.[75]

Through receptor-mediated endocytosis, the transferrin receptor, which is widely expressed on brain capillary endothelial cells, promotes iron uptake into the brain. Hence, surface functionalization of nanoparticles with transferrin has been widely used for transport across the BBB.[76] For example, transferrin-conjugated solid lipid nanoparticles loaded with rivastigmine demonstrated 2-fold higher brain drug levels compared to normal SLN after intravenous administration in rats. Similarly, lactoferrin receptors are also expressed on the BBB and have been explored for nanoparticle targeting. Lactoferrin-anchored PEG-PLGA nanoparticles could deliver loperamide across the BBB in in vitro models. Co-functionalization with transferrin and lactoferrin on bovine serum albumin nanoparticles led to greater permeation across the BBB compared to nanoparticles with a single ligand in an in vitro model.[77] Cell-penetrating peptides like TAT have also been investigated for crossing the BBB via adsorptive-mediated endocytosis. TAT-conjugated liposomes loaded with an antioxidant enzyme showed increased

delivery across the BBB and neuroprotective effects in ischemia-reperfusion injury mice models.[78]

B. Imaging and Diagnosis

1. Nanoparticle-based imaging agents:

In order to diagnose and track neuroinflammatory diseases such as multiple sclerosis, super paramagnetic iron oxide nanoparticles have been utilized extensively as MRI contrast agents. The iron oxide nanoparticles improve contrast in T2-weighted MRI images by reducing the protons' T2 relaxation durations. High accumulations of nanoparticles at inflammatory foci result in signal reduction in MRI. Gold nanoparticles provide significant contrast enhancement for computed tomography (CT) imaging.[79]The high atomic number of gold leads to strong X-ray attenuation. Gold nanoparticles functionalized with BBB-targeting peptides like cRVG accumulated in the brain upon intravenous injection and showed over 3-fold greater CT contrast. Quantum dots are fluorescent semiconductor Nano crystals that can trace abnormal protein aggregation pathways in the brain. Near-infrared-emitting quantum dots coated with antibodies specific to amyloid beta plaques demonstrated labelling of plaques in post-mortem human Alzheimer's brain tissues.

2. Early detection and diagnostic applications:

The large surface area to volume ratio of nanoparticles allows the creation of sensitive surface-based bio sensing assays for neurodegenerative disease biomarkers. [81] Magnetic nanoparticles modified with antibodies detected amyloid beta oligomers at Pico molar concentrations in plasma samples from Alzheimer's patients.[82] Plasmonic gold nanoparticles exhibit surface plasmon resonance, allowing detection of subtle changes in the local environment. This was leveraged to develop aggregation assays for alpha-synuclein, which could differentiate Parkinson's patients from healthy controls.[83]

C. Neuroprotection and Regeneration

1. Neuroprotective effects of nanomaterials:

Nanomaterial's like dendrimers, cerium oxide nanoparticles, and carbon nanotubes have been investigated for their innate antioxidant properties that can help mitigate oxidative stress associated with neurodegenerative diseases. For example, a study by [84] found that glyconanoparticles called Sweet-Iron modified with antioxidants were able to decrease reactive oxygen species generation and provided neuroprotection in cell models of Parkinson's disease. The antioxidant glyconanoparticles sequestered iron ions and reduced their participation in Fenton reactions, which generate free radicals. Similarly, platinum nanoparticles were also

able to act as free radical scavengers. According to research, by pre-treating neuronal cell cultures with platinum nanoparticles, they could decrease apoptosis and oxidative damage induced by toxins used in experimental models of Parkinson's disease.[85]

2. Nanotechnology for neural regeneration:

Aligned nanofibers fabricated from materials like collagen, fibrin, and hyaluronic acid provide contact guidance cues, mimicking the native extracellular matrix. [86] This promotes directional adhesion and axonal extension along the long axis of the fibres. Transplantation of BDNF-loaded collagen nanofibers in hemisected spinal cord injury models demonstrated significant axonal regrowth. Gelatin-siloxane nanoparticles loaded with miR-124 transfected neural stem cells and stimulated neuronal differentiation in cell culture models of Huntington's disease.[87] Conjugation of nanoparticles with cell-penetrating and targeting peptides enhanced intracellular delivery.

- **Challenges and Future Perspectives:**

Current challenges in nanomedicine for neurodegenerative disorders:

One of the major challenges is the ability to cross the blood-brain barrier (BBB) efficiently using Nano carriers. The BBB has very tight junctions that restrict the permeation of most molecules and needs to be crossed without disrupting it. [88] Although ligands like transferrin have been used, in vivo delivery across the BBB needs further improvement.

Another key challenge is potential long-term toxicity and accumulation of nanomaterials in the body.[89]The interactions of nanoparticles with the immune system and the effects of their accumulation in organs like the liver and spleen require extensive evaluation to ensure safety. Biocompatible and biodegradable materials could help mitigate adverse effects.

Targeted delivery of Nano therapeutics specifically to the site of neurodegeneration is also challenging. [90] Most approaches rely on passive targeting based on enhanced permeation effects. Active targeted delivery to specific cell types affected in the brain remains elusive and needs innovative targeting moieties.

Scale-up of nanoparticle fabrication methods from lab to industry while retaining the desirable Nano scale properties is not trivial. [91] Maintaining reproducibility and quality control during mass production requires significant process optimization and control.

- **Future directions and potential breakthroughs:**

Advanced biomimetic Nano carriers could replicate properties of cell membranes and exhibit enhanced circulation times,

biocompatibility, and the ability to cross the blood-brain barrier (BBB). For example, supported bilayer lipid membranes on Nano porous silica nanoparticles may act as cell-like transporters [92].

Novel targeting moieties need to be explored for active transport across the BBB as well as targeted delivery to specific cells and subcellular compartments affected in neurodegeneration.[93] Peptide sequences identified through phage display and envelope proteins from viruses that cross the BBB could provide exciting options.

Combination Nano therapies co-delivering multiple drugs with synergistic mechanisms tailored to interrupt different neurodegenerative pathways could provide more efficacious treatment and delay disease progression. [94] For instance, co-delivery of anti-amyloid and anti-inflammatory drugs.

Advances in micro fabrication techniques like 3D printing and lithography can aid in the precision engineering of Nano carriers with controlled shape, size, and release characteristics to match specific application needs.

Leveraging newer modalities like CRISPR/Cas9 gene editing has the potential for repairing and silencing mutant genes implicated in neurodegeneration using Nano delivery systems.

Integration of theranostic Nanomedicine capable of simultaneous imaging, diagnosis, and therapy in neurodegenerative diseases could enable real-time guided personalized therapy.[95]

CONCLUSION:

The therapy of neurodegenerative diseases may benefit greatly from nanomedicine. Nano scale materials are perfect for delivering therapeutic compounds directly to the site of disease because of their special qualities, which include their capacity to target certain regions of the brain and pass the blood-brain barrier. Even though this sector has seen a lot of progress, there are still obstacles to be addressed, such as possible toxicity, moral dilemmas, and the requirement for additional scientific trials to confirm the efficacy and safety of these treatments. Notwithstanding these obstacles, nanomedicine appears to have a bright future in the treatment of neurodegenerative diseases. It is envisaged that as research advances, nanomedicine will result in more potent therapies for neurodegenerative diseases, enhancing patients' quality of life and possibly even bringing about a cure.

To sum up, nanomedicine is a fresh and exciting strategy to get over the present restrictions in the management of neurodegenerative diseases. It has the potential to completely transform neurology and greatly enhance patient outcomes with more study and advancement.

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REFERENCES:

[1] Mayeux R. Epidemiology of neurodegeneration. Annual Review of Neuroscience. 2003 Mar;26(1):81-104.

[2] Querfurth HW, LaFerla FM. Mechanisms of disease. N Engl J Med. 2010;362(4):329-44.

[3] Skovronsky DM, Lee VM, Trojanowski JQ. Neurodegenerative diseases: new concepts of pathogenesis and their therapeutic implications. Annu. Rev. Pathol. Mech. Dis. 2006 Feb 28;1(1):151-70.

[4] 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. Journal of Controlled Release. 2016 Aug 10;235:34-47.

[5] Ding Y, Wang Y, Hu Q. Recent advances in overcoming barriers to cell-based delivery systems for cancer immunotherapy. In Exploration 2022 Jun (Vol. 2, No. 3, p. 20210106).

[6] Pardridge WM. The blood-brain barrier: bottleneck in brain drug development. NeuroRx. 2005 Jan;2:3-14.

[7] Spector R. Drug transport in the mammalian central nervous system: multiple complex systems: a critical analysis and commentary. Pharmacology. 2000 Feb 16;60(2):58-73.

[8] Alyaudtin RN, Reichel A, Löbenberg R, Ramge P, Kreuter J, Begley DJ. Interaction of poly(butylcyanoacrylate) nanoparticles with the blood-brain barrier in vivo and in vitro. Journal of Drug Targeting. 2001 Jan 1; 9(3): 209-21.

[9] Pardridge WM. Drug and gene delivery to the brain: the vascular route. Neuron. 2002 Nov 14;36(4):555-8.

[10] Banks WA, Le Bel CP. Strategies for the delivery of leptin to the CNS. Journal of Drug Targeting. 2002 Jan 1;10(4):297-308.

[11] Liu G, Garrett MR, Men P, Zhu X, Perry G, Smith MA. Nanoparticle and other metal chelation therapeutics in Alzheimer's disease. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2005 Sep 25;1741(3):246-52.

[12] Garcia-Garcia E, Andrieux K, Gil S, Couvreur P. Colloidal carriers and blood–brain barrier (BBB) translocation: a way to deliver drugs to the brain?. International Journal of Pharmaceutics. 2005 Jul 25;298(2):274-92.

[13] Querfurth HW, LaFerla FM. Mechanisms of disease. N Engl J Med. 2010;362(4):329-44.

[14] Jack CR, Holtzman DM. Biomarker modeling of Alzheimer's disease. Neuron. 2013 Dec 18;80(6):1347-58.

[15] Porsteinsson AP, Isaacson RS, Knox S, Sabbagh MN, Rubino I. Diagnosis of early Alzheimer's disease: clinical practice in 2021. The journal of prevention of Alzheimer's disease. 2021 Mar;8:371-86.

[16] van der Lee SJ, Wolters FJ, Ikram MK, Hofman A, Ikram MA, Amin N, van Duijn CM. The effect of APOE and other common genetic variants on the onset of Alzheimer's disease and dementia: a community-based cohort study. The Lancet Neurology. 2018 May 1;17(5):434-44.

[17] Patterson C. Alzheimer's Disease International World Alzheimer Report 2018—The State of the Art of Dementia Research. Alzheimer's Disease International: London, UK. 2018.

[18] Babapour Mofrad R, Tijms BM, Scheltens P, Barkhof F, van der Flier WM, Sikkes SA, Teunissen CE. Sex differences in CSF biomarkers vary by Alzheimer disease stage and APOE ε4 genotype. Neurology. 2020 Oct 27;95(17):e2378-88.

[19] Gustavsson AM, Van Westen D, Stomrud E, Engström G, Nägga K, Hansson O. Midlife atherosclerosis and development of Alzheimer or vascular dementia. Annals of Neurology. 2020 Jan; 87(1): 52-62.

[20] Forno LS. The Neuropathology Of Parkinson'S Disease: The Lewy body as a clue to the nerve cell degeneration. Progress in Parkinson research. 1988:11-21.

[21] Braak H, Del Tredici K, Rüb U, De Vos RA, Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiology of aging. 2003 Mar 1;24(2):197-211.

[22] Thomas B, Beal MF. Parkinson's disease. Human molecular genetics. 2007 Oct 15;16(R2):R183-94.

[23] Bruyn GW. Huntington's chorea In: Vinken PJ, Bruyn GW (eds) Handbook of clinical neurology.

[24] MacDonald ME, Ambrose CM, Duyao MP, Myers RH, Lin C, Srinidhi L, Barnes G, Taylor SA, James M, Groot N, MacFarlane H. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell. 1993 Mar 26;72(6):971-83.

[25] Bates G. Huntingtin aggregation and toxicity in Huntington's disease. The Lancet. 2003 May 10;361(9369):1642-4.

[26] Kiernan MC, Vucic S, Cheah BC, Turner MR, Eisen A, Hardiman O, Burrell JR, Zoing MC. Amyotrophic lateral sclerosis. The lancet. 2011 Mar 12;377(9769):942-55.

[27] Khouzam HR. The Psychiatric Manifestations of Multiple Sclerosis and Their Treatment. Journal of Spine Research & Reports. SRC/JSRR-104. DOI: doi.org/10.47363/JSRR/2022 (1). 2022;103.

[28] Vieira RT, Caixeta L, Machado S, Silva AC, Nardi AE, Arias-Carrión O, Carta MG. Epidemiology of early-onset dementia: a review of the literature. Clinical practice and epidemiology in mental health: CP & EMH. 2013;9:88.

[29] Rabinovici GD, Miller BL. Frontotemporal lobar degeneration: epidemiology, pathophysiology, diagnosis, and management. CNS drugs. 2010 May; 24:375-98.

[30] Rohrer JD, Guerreiro R, Vandrovcova J, Uphill J, Reiman D, Beck J, Isaacs AM, Authier A, Ferrari R, Fox NC, Mackenzie IR.

The heritability and genetics of frontotemporal lobar degeneration. Neurology. 2009 Nov 3;73(18):1451-6.

[31] Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy: a heterogeneous degeneration involving the brain stem, basal ganglia, and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia, and dementia. Archives of Neurology. 1964 Apr 1;10(4):333-59.

[32] Bigio EH, Brown DF, White III CL. Progressive supranuclear palsy with dementia: cortical pathology. Journal of Neuropathology and Experimental Neurology. 1999 Apr 1;58(4):359-64.

[33] Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy: a heterogeneous degeneration involving the brain stem, basal ganglia, and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia, and dementia. Archives of Neurology. 1964 Apr 1;10(4):333-59.

[34] Josephs KA, Boeve BF, Duffy JR, Smith GE, Knopman DS, Parisi JE, Petersen RC, Dickson DW. Atypical progressive supranuclear palsy underlying progressive apraxia of speech and nonfluent aphasia. Neurocase. 2005 Aug 1;11(4):283-96.

[35] Williams DR, de Silva R, Paviour DC, Pittman A, Watt HC, Kilford L, Holton JL, Revesz T, and Lees AJ. Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. Brain. 2005 Jun 1;128(6):1247-58.

[36] Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, Boxer AL, Dickson DW, Grossman M, Hallett M, Josephs KA. Criteria for the diagnosis of corticobasal degeneration. Neurology. 2013 Jan 29;80(5):496-503.

[37] Kouri N, Murray ME, Hassan A, Rademakers R, Uitti RJ, Boeve BF, Graff-Radford NR, Wszolek ZK, Litvan I, Josephs KA, Dickson DW. Neuropathological features of corticobasal degeneration presenting as corticobasal syndrome or Richardson syndrome. Brain. 2011 Nov 1;134(11):3264-75.

[38] Boeve BF. The multiple phenotypes of corticobasal syndrome and corticobasal

degeneration: implications for further study. Journal of Molecular Neuroscience. 2011 Nov; 45:350-3.

[39] Rebeiz JJ, Kolodny EH, Richardson EP. Corticodentatonigral degeneration with neuronal achromasia. Archives of Neurology. 1968 Jan 1; 18(1): 20-33.

[40] Bastian FO. Creutzfeldt-Jakob disease and other transmissible spongiform encephalopathies. (No Title). 1991.

[41] Will RG. Epidemiology of Creutzfeldt-Jakob disease. British Medical Bulletin. 1993 Oct 1;49(4):960-70.

[42] Paulson HL, Shakkottai VG, Clark HB, Orr HT. Polyglutamine spinocerebellar ataxias—from genes to potential treatments. Nature Reviews Neuroscience. 2017 Oct;18(10):613-26.

[43] Schöls L, Bauer P, Schmidt T, Schulte T, Riess O. Autosomal dominant cerebellar ataxias: clinical features, genetics, and pathogenesis. The Lancet Neurology. 2004 May 1;3(5):291-304.

[44] Diallo A, Jacobi H, Cook A, Labrum R, Durr A, Brice A, Charles P, Marelli C, Mariotti C, Nanetti L, Panzeri M. Survival in patients with spinocerebellar ataxia types 1, 2, 3, and 6 (EUROSCA): a longitudinal cohort study. The Lancet Neurology. 2018 Apr 1;17(4):327-34.

[45] Müller T, Langner C, Fuchsbichler A, Heinz-Erian P, Ellemunter H, Schlenck B, Bavdekar AR, Pradhan AM, Pandit A, Müller-Höcker J, Melter M. Immunohistochemical analysis of Mallory bodies in Wilsonian and non-Wilsonian hepatic copper toxicosis. Hepatology. 2004 Apr;39(4):963-9.

[46] Strand S, Hofmann WJ, Grambihler A, Hug H, Volkmann M, Otto G, Wesch H, Mariani SM, Hack V, Stremmel W, Krammer PH. Hepatic failure and liver cell damage in acute Wilson's disease involve CD95 (APO-1/Fas)-mediated apoptosis. Nature medicine. 1998 May 1;4(5):588-93.

[47] Lupski JR, de Oca-Luna RM, Slaugenhaupt S, Pentao L, Guzzetta V, Trask BJ, Saucedo-Cardenas O, Barker DF, Killian JM, Garcia CA, Chakravarti A. DNA duplication associated with Charcot-Marie-Tooth disease type

1A. Cell. 1991 Jul 26;66(2):219-32.

[48] Pareyson D, Marchesi C. Diagnosis, natural history, and management of Charcot–Marie–Tooth disease. The Lancet Neurology. 2009 Jul 1;8(7):654-67.

[49] D'Amico A, Mercuri E, Tiziano FD, Bertini E. Spinal muscular atrophy. Orphanet Journal of Rare Diseases. 2011 Dec; 6:1-0.

[50] Lorson CL, Rindt H, Shababi M. Spinal muscular atrophy: mechanisms and therapeutic strategies. Human molecular genetics. 2010 Apr 15;19(R1):R111-8.

[51] Finkel RS, McDermott MP, Kaufmann P, Darras BT, Chung WK, Sproule DM, Kang PB, Foley AR, Yang ML, Martens WB, Oskoui M. Observational study of spinal muscular atrophy type I and implications for clinical trials. Neurology. 2014 Aug 26;83(9):810-7.

[52] Friedreich N. Ueber necrose der nierenpapillen bei hydronephrose. Archiv für pathologische Anatomie und Physiologie und für klinische Medicin. 1877 Feb;69(2):308-12.

[53] Hodge G. Three Cases of Friedreich's Disease All Presenting Marked Increase of the Knee-Jerk. British Medical Journal. 1897 Jun 6;1(1901):1405.

[54] McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, Cummings J, Duda JE, Lippa C, Perry EK, Aarsland D. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology. 2005 Dec 27;65(12):1863-72.

[55] Xia Y, Xiong Y, Lim B, Skrabalak SE. Shape-controlled synthesis of metal Nano crystals: simple chemistry meets complex physics?. Angewandte Chemie International Edition. 2009 Jan;48(1):60-103.

[56] Sajja HK, East MP, Mao H, Wang YA, Nie S, Yang L. Development of multifunctional nanoparticles for targeted drug delivery and noninvasive imaging of therapeutic effect. Current drug discovery technologies. 2009 Mar 1; 6(1): 43-51.

[57] Bharali DJ, Mousa SA. Emerging Nanomedicine for early cancer detection and improved treatment: current perspective and future promise. Pharmacology & therapeutics. 2010 Nov 1;128(2):324-35.

[58] Bhaskar S, Tian F, Stoeger T, Kreyling W, de la Fuente JM, Grazú V, Borm P, Estrada G,

Ntziachristos V, Razansky D. Multifunctional Nano carriers for diagnostics, drug delivery, and targeted treatment across the blood-brain barrier: perspectives on tracking and neuroimaging. Particle and fiber toxicology. 2010 Dec; 7:1-25.

[59] Friberg S, Nyström AM. NANOMEDICINE: Will it offer possibilities to overcome multiple drug resistance in cancer?. Journal of Nanobiotechnology. 2016 Dec;14:1-7.

[60] Galvin P, Thompson D, Ryan KB, McCarthy A, Moore AC, Burke CS, Dyson M, MacCraith BD, Gun'ko YK, Byrne MT, Volkov Y. Nanoparticle-based drug delivery: case studies for cancer and cardiovascular applications. Cellular and Molecular Life Sciences. 2012 Feb;69:389-404.

[61] Poirot-Mazères I. Chapitre 6. Legal aspects of the risks raised by nanotechnologies in the field of medicine. Journal international de bioéthique. 2011;22(1):99-118.

[62] Carlesi C, Pasquali L, Piazza S, Gerfo AL, Ienco EC, Alessi R, Fornai F, Siciliano G. Strategies for a clinical approach to neurodegeneration in amyotrophic lateral sclerosis. Archives italiennes de biologie. 2011 Mar 10;149(1):151-67.

[63] 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. Journal of Controlled Release. 2016 Aug 10;235:34-47.

[64] Dhamija P, Mehata AK, Setia A, Priya V, Malik AK, Bonlawar J, Verma N, Badgujar P, Randhave N, Muthu MS. Nanotheranostics: molecular diagnostics and nanotherapeutic evaluation by photoacoustic/ultrasound imaging in small animals. Molecular pharmaceutics. 2023 Nov 6;20(12):6010-34.

[65] Sandhir R, Yadav A, Sunkaria A, Singhal N. Nano-antioxidants: An emerging strategy for intervention against neurodegenerative conditions. Neurochemistry International. 2015 Oct 1;89:209-26.

[66] Almatroodi SA, Almatroudi A, Khan AA, Alhumaydhi FA, Alsahli MA, Rahmani AH. Potential therapeutic targets of epigallocatechin gallate (EGCG), the most abundant catechin in green tea, and its role in the therapy of various types of cancer.

Molecules. 2020 Jul 9; 25(14):3146.

[67] Park JS, Kim ST, Kim SY, Jo MG, Choi MJ, Kim MO. A novel kit for early diagnosis of Alzheimer's disease using fluorescent nanoparticle imaging. Scientific Reports. 2019 Sep 12; 9(1): 13184.

[68] Meng J, Guo F, Xu H, Liang W, Wang C, Yang XD. Combination therapy using co-encapsulated resveratrol and paclitaxel in liposomes for drug resistance reversal in breast cancer cells in vivo. Scientific Reports. 2016 Mar 7; 6(1):22390.

[69] Wong HL, Bendayan R, Rauth AM, Li Y, Wu XY. Chemotherapy with anticancer drugs encapsulated in solid lipid nanoparticles. Advanced drug delivery reviews. 2007 Jul 10;59(6):491-504.

[70] 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. Journal of Controlled Release. 2016 Aug 10;235:34.

[71] Rahman MM, Kotturi H, Nikfarjam S, Bhargava K, Ahsan N, Khandaker M. Antimicrobial Activity of Polycaprolactone Nanofiber Coated with Lavender and Neem Oil Nanoemulsions against Airborne Bacteria. Membranes. 2024 Jan 29;14(2):36.

[72] Salatin S, Barar J, Barzegar-Jalali M, Adibkia K, Milani MA, Jelvehgari M. Hydrogel nanoparticles and nanocomposites for nasal drug/vaccine delivery. Archives of pharmacal research. 2016 Sep;39:1181-92.

[73] Jain P, Parikh S, Patel P, Shah S, Patel K. Comprehensive Insights into Herbal P-Glycoprotein Inhibitors and Nanoformulations for Improving Anti-Retroviral Therapy Efficacy. Journal of Drug Targeting. 2024 May 15 (just-accepted): 1-64.

[74] Ulbrich K, Knobloch T, Kreuter J. Targeting the insulin receptor: nanoparticles for drug delivery across the blood–brain barrier (BBB). Journal of Drug Targeting. 2011 Feb 1; 19(2): 125-32.

[75] Mahajan HS, Mahajan MS, Nerkar PP, Agrawal A. Nanoemulsion-based intranasal drug delivery system of saquinavir mesylate for brain targeting. Drug delivery. 2014 Mar 1; 21(2): 148-54.

[76] Liu Y, Huang R, Han L, Ke W, Shao K, Ye L, Lou J, Jiang C. Brain-targeting gene delivery and cellular internalization

mechanisms for modified rabies virus glycoprotein RVG29 nanoparticles. Biomaterials. 2009 Sep 1;30(25):4195-202.

[77] Naha PC, Al Zaki A, Hecht E, Chorny M, Chhour P, Blankemeyer E, Yates DM, Witschey WR, Litt HI, Tsourkas A, Cormode DP. Dextran-coated bismuth–iron oxide nanohybrid contrast agents for computed tomography and magnetic resonance imaging. Journal of Materials Chemistry B. 2014;2(46):8239-48.

[78] Ivask A, Pilkington EH, Blin T, Käkinen A, Vija H, Visnapuu M, Quinn JF, Whittaker MR, Qiao R, Davis TP, Ke PC. Uptake and transcytosis of functionalized super paramagnetic iron oxide nanoparticles in an in vitro blood-brain barrier model. Biomaterials science. 2018;6(2):314-23.

[79] Cao J, Wu J, Mu J, Feng S, Gao J. The design criteria and therapeutic strategy of functional scaffolds for spinal cord injury repair. Biomaterials Science. 2021;9(13):4591-606.

[80] Melnik BC, Stremmel W, Weiskirchen R, John SM, Schmitz G. Exosome-Derived MicroRNAs of Human Milk and Their Effects on Infant Health and Development. Biomolecules 2021, 11, 851 [Internet]. 2021.

[81] Brown RE. Genetically modified mice for research on human diseases: A triumph for biotechnology or a work in progress?. The EuroBiotech Journal. 2022;6(2):61-88.

[82] Savic R, Zheng J, Allen C, Maysinger D. Nanomedicine Coming of Age: Recent Developments in Nanoneuroscience and Nano-Oncology. Polymeric Biomaterials. 2020 Mar 5:1279-310.

[83] Sagnou M, Mavroidi B, Kaminari A, Boukos N, Pelecanou M. Novel isatin thiosemicarbazone derivatives as potent inhibitors of β-amyloid peptide aggregation and toxicity. ACS Chemical Neuroscience. 2020 Jun 29;11(15):2266-76.

[84] Ji WC, Li M, Jiang WT, Ma X, Li J. Protective effect of brain-derived neurotrophic factor and neurotrophin-3 overexpression by adipose-derived stem cells combined with silk fibroin/chitosan scaffold in spinal cord injury. Neurological Research. 2020 May 3; 42(5): 361-71.

[85] Chen H, Li N, Cai Y, Ma C, Ye Y, Shi X, Guo J, Han Z, Liu Y, Wei X.

Exosomes in neurodegenerative diseases: therapeutic potential and modification methods. Neural Regeneration Research: 10-4103.

[86] Jena L, McErlean E, McCarthy H. Delivery across the blood-brain barrier: nanomedicine for glioblastoma multiforme. Drug delivery and translational research. 2020 Apr;10:304-18.

[87] Manivasagan P, Bharathiraja S, Moorthy MS, Oh YO, Seo H, Oh J. Marine biopolymer-based nanomaterial's as a novel platform for theranostic applications. Polymer Reviews. 2017 Oct 2;57(4):631-67.

[88] Rahman HS, Othman HH, Hammadi NI, Yeap SK, Amin KM, Abdul Samad N, Alitheen NB. Novel drug delivery systems for loading natural plant extracts and their biomedical applications. International Journal of Nanomedicine. 2020 Apr 15:2439-83.

[89] Mohammadpour-Haratbar A, Zare Y, Rhee KY. A review on drug delivery systems containing polymer nanocomposites for breast cancer treatment. Polymer Reviews. 2024 Apr 2;64(2):490-527.

[90] Wu X, Cui X, Wang Q, Wang J, Wu W, Li W, Jiang Z. Manipulating the cross-layer channels in gC 3 N 4 nanosheet membranes for enhanced molecular transport. Journal of Materials Chemistry A. 2021;9(7):4193-202.

[91] Del Amo L, Cano A, Ettcheto M, Souto EB, Espina M, Camins A, García ML, Sánchez-López E. Surface functionalization of PLGA nanoparticles to increase transport across the BBB for Alzheimer's disease. Applied Sciences. 2021 May 10; 11(9): 4305.

[92] Zhang Z, Zheng M, Liu C, Zhuang X. Frontiers in Bioengineering and Biotechnology. REVIEW published: 19 July 2022. Advanced Bioactive Nanomaterial's for Diagnosis and Treatment of Major Chronic Diseases. 2023 Oct 30:4.

[93] Wang Z, Liang X, Wang G, Wang X, Chen Y. Emerging bioprinting for wound healing. Advanced Materials. 2023 Aug 11:2304738.

[94] Zhai LM, Zhao Y, Xiao RL, Zhang SQ, Tian BH, Li XX, Zhang R, Ma RS, Liang HX. Nuclear-targeted carbon quantum dot-mediated CRISPR/Cas9 delivery for fluorescence visualization and

efficient editing. Nano scale. 2022;14(39):14645-60.

[95] Sun D. Nanotheranostics: integration of imaging and targeted drug delivery. Molecular Pharmaceutics. 2010 Dec 6; 7(6): 1879.

Abbreviation

Abbreviation	Full Form
ALS	Amyotrophic lateral sclerosis
siRNA	small interfering ribonucleic acid
mRNA	Messenger Ribonucleic acid
DNA	Deoxyribonucleic acid
CNS	Central nervous system
MS	Multiple sclerosis
PSP	Progressive supranuclear palsy
CBD	Corticobasal degeneration
CJD	Creutzfeldt-Jakob disease
SMA	Spinal muscular atrophy
AD	Alzheimer's disease
SNpc	substantianigra pars compacta
LB	Lewy bodies
HD	Huntington’s disease
SCA	Spinocerebellar ataxias
CMT	Charcot-Marie-tooth
SMN	Survival motor neuron
FRDA	Friedreich ataxia
Np’s	Nanoparticles
MRI	Magnetic Resonance Imaging
QDs	Quantum Dots
PD	Parkinson disease
NDs	Neurodegenerative diseases
COMT	catechol-O-methyltransferase
BBB	Blood Brain Barrier
SLN	Solid Lipid Nanoparticles
NLC	Nanostructured Lipid Carriers