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Chapter 2: Nanotechnology in Neuroscience Transforming Alzheimer's Therapy

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Abstract

Alzheimer's disease (AD) is the most prevalent form of dementia, characterized by progressive memory loss, cognitive decline, and functional impairment, imposing a profound socioeconomic and healthcare burden worldwide. Current pharmacological treatments, primarily cholinesterase inhibitors and NMDA receptor antagonists, provide only symptomatic relief without halting neurodegeneration, largely due to challenges such as poor bioavailability, limited blood–brain barrier (BBB) penetration, and systemic side effects. In recent years, nanotechnology has emerged as a transformative strategy to overcome these barriers by enabling targeted drug delivery, improved solubility, controlled release, and enhanced BBB transport. A diverse range of nanocarriers—including metallic nanoparticles (gold, silver, cerium oxide), polymeric systems (PLGA, chitosan), lipid-based vesicles (liposomes, solid lipid nanoparticles, nanoemulsions), carbon nanomaterials, and dendrimers—have been investigated for their ability to deliver anti-Alzheimer's agents, inhibit amyloid-β aggregation, stabilize tau proteins, and reduce oxidative stress. Functionalization strategies further enhance targeting specificity, reduce off-target effects, and improve therapeutic outcomes. Nanodiagnostic platforms, including imaging-enhanced nanoparticles and biosensors, also provide early detection opportunities, critical for timely intervention. Despite promising preclinical outcomes, translational challenges such as long-term toxicity, large-scale reproducibility, and regulatory approval remain significant hurdles. Emerging approaches integrating nanomedicine with personalized therapy, exosome-based delivery, and AI-guided design highlight future potential in achieving disease-modifying treatments for AD. This review consolidates current advances in nanotechnology-based interventions for AD,

emphasizing their role in diagnosis, drug delivery, and future perspectives, while addressing the challenges that must be overcome to enable clinical translation.

Keywords: *Alzheimer's disease, nanotechnology, blood–brain barrier, nanoparticles, targeted drug delivery, neurodegeneration.*

1. Introduction

1.1 The Global Burden of Alzheimer's Disease (AD)

Alzheimer's Disease (AD) is a progressive and irreversible neurological condition that leads to cognitive decline and dementia. It is the most common cause of dementia worldwide. AD currently affects 32.6 million individuals globally, and without effective treatments, this number is projected to reach 78 million by 2030 and 139 million by 2050. This increasing prevalence poses significant health, societal, and economic challenges [1].

Alzheimer's disease (AD) is a neurodegenerative condition that develops over time and impairs cognitive and behavioural abilities. It is named after Alois Alzheimer who first characterized AD in 1906. The two main categories of amyloid disease are sporadic AD (SAD) and familial AD (FAD). Gene mutations in amyloid percussor protein (APP), presenilin 1 (PSEN1), and presenilin (PSEN2) are responsible for the occurrence of FAD, whereas ageing, genetics, metabolism, and environmental factors interact intricately to cause SAD. Every AD patient experiences 3 stages in their life cycle that includes a mild stage where the people get memory loss, speech difficulties and mood changes followed by a moderate stage where they experience a learning impairment, dementia and aggressive behaviours and a final severe stage in which they feel bed ridden and motor impaired. The buildup of neurofibrillary tangles and amyloid β in the hippocampus causes Alzheimer's disease. Different stages and types of alzhimers are presented in the fig-2.1 below[2].

The disease leads to the death of brain cells, resulting in memory loss and a decline in behavioural, mental, and intellectual abilities. Memory impairment, particularly the inability to recall recent events, is often the first symptom, progressing to the loss of long-term memory as the disease advances. AD is unequivocally confirmed post-mortem by brain atrophy associated with extracellular amyloid-beta plaques and intraneuronal neurofibrillary tangles (NFTs) of hyperphosphorylated tau protein. These lesions initially appear in the hippocampus and entorhinal cortex, later spreading to other cortical areas. Risk factors for AD include aging, unhealthy diet, lifestyle, cardiovascular factors (hypertension, diabetes, atherogenic dyslipidaemia, obesity), environmental toxicants, genetic factors, mutation, and trauma [3].

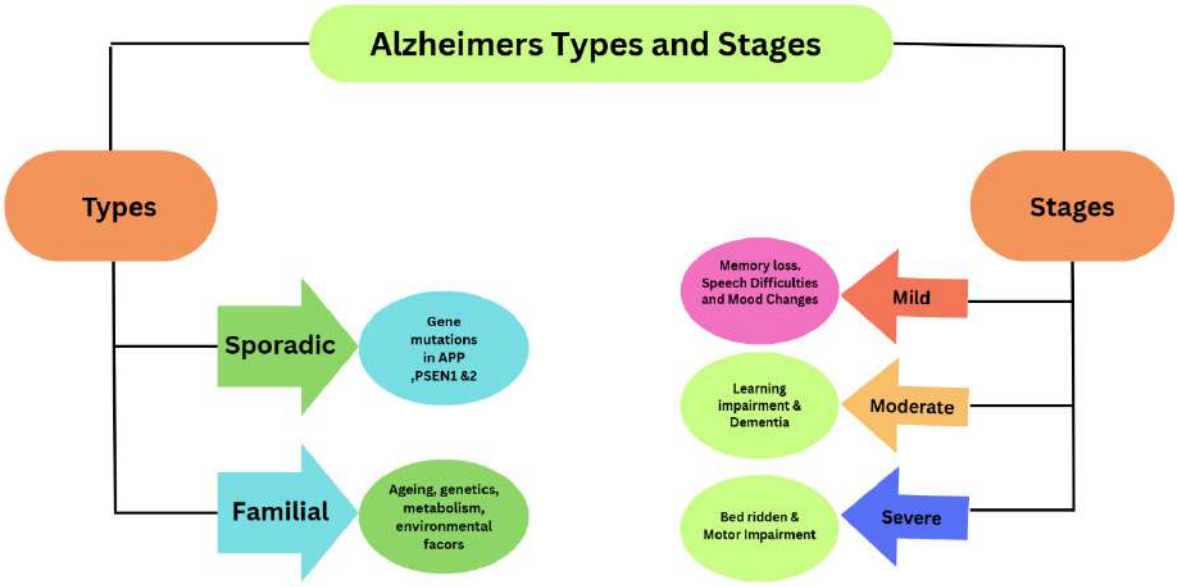

Figure- 2.1: Different stages and types of Alzheimers

1.2 Limitations of Current AD Therapies

Currently, there is no cure for AD in humans; treatments are only symptomatic. Existing therapies enhance cognitive abilities and temporarily relieve symptoms but do not halt or slow the disease's development. Conventional AD drugs, such as NMDA receptor antagonists and cholinesterase inhibitors, primarily aim to enhance cholinergic transmission in the brain. However, these conventional oral dosage forms face several limitations, including poor absorption in neuronal cell membranes, instability, neurotoxicity, first-pass metabolism, un favorable pharmacokinetics, and systemic adverse effects. These limitations lead to lower bioavailability, require high drug doses, and often result in poor patient compliance.

A major physiological obstacle for drug delivery to the brain is the blood-brain barrier (BBB). The BBB restricts the movement of most therapeutic compounds, allowing only lipophilic molecules smaller than 400 Da to cross. The physicochemical properties of drugs, such as solubility, molecular weight, polarity, and partition coefficient, are critical for therapeutic effect, and suboptimal properties can lead to drug failure. Immunotherapy approaches for AD have also shown high failure rates in clinical trials, often due to uneven outcomes or significant side effects like meningoencephalitis [4].

1.3 Emergence of Nanotechnology in Biomedical Applications

Nanotechnology, which involves manipulating matter at the nanoscale (1 to 100 nm), offers a novel and transformative approach to biomedical applications, including diagnostics and therapies for complex diseases. Nanomaterials, particularly nanoparticles (NPs), are well-suited for interacting with biomolecules and cells due to their size similarity to proteins and nucleic acids. They offer advantages such as a high surface-to-volume ratio, which is beneficial for biological recognition and sensing.

Nanotechnology enables new possibilities for diagnosing, treating, and potentially curing human diseases. NPs can be engineered to specifically target diseased cells, delivering drugs or other therapeutic agents directly to the disease site. This technology has shown promise in improving drug delivery, diagnosis, and tissue repair in various neurological disorders. Nanomedicine aims to overcome BBB difficulties and address the unique complexity of neurological diseases, providing effective drug delivery through targeted and controlled release with reduced adverse effects [5]. Linking to these limitations of current Alzheimer's therapy are mentioned in table-2.1 below

1.4 Bridging Neuroscience and Nanotechnology for AD Treatment

Integrating clinical neuroscience with nanoscience holds the potential to revolutionize AD diagnosis and therapy. Nanotechnology offers solutions to major challenges in AD treatment, such as early diagnosis and effective drug delivery across the BBB. Nanomaterials are currently under intense study for their potential to manage AD pathologies. Nanotechnology can aid in the early detection of AD via highly efficient signal transduction methods. The development of nanotechnology has facilitated the advanced treatment of AD, showing excellent potential for improving the brain-targeting of drugs [6].

Table 2.1: Limitations of Current Alzheimer's Disease Therapies

Limitation Category	Specific Issues
Drug Properties	Poor absorption in neuronal cell membranes, instability, neurotoxicity, unfavorable pharmacokinetics, require high drug doses, suboptimal physicochemical properties (solubility, molecular weight, polarity, partition coefficient) can lead to drug failure.
Metabolism & Side Effects	First-pass metabolism, systemic adverse effects, lower bioavailability, poor patient compliance.
Brain Accessibility	Major physiological obstacle: Blood-Brain Barrier (BBB). BBB restricts most therapeutic compounds, allowing only lipophilic molecules smaller than 400 Da to cross.
Clinical Trial Outcomes	Immunotherapy approaches show high failure rates, often due to uneven outcomes or significant side effects like meningoencephalitis.

2. Fundamentals of Nanotechnology for Neurological Applications

2.1 Defining Nanomaterials: Types and Properties

Nanomaterials are defined as materials with at least one dimension falling between 1 and 100 nm. At this scale, materials often exhibit unique properties, such as super para magnetism or surface plasmon resonance, that are highly interesting to the medical community. Due to their size similarity to biomolecules like proteins and nucleic acids, nanomaterials, particularly nanoparticles (NPs), are well-suited for interacting with these biological entities and, consequently, with cells. Their large surface-to-volume ratio also offers significant benefits in biological recognition applications, especially in sensing. These compounds have undergone extensive testing for therapeutic uses. General properties and characteristics of nanomaterials suitable for biomedical applications are mentioned in below table 2.2.

Table 2.2: General Properties of Nanomaterials Relevant to Biomedical Applications

Property	Advantage
Size	1 to 100 nm. Similar to proteins and nucleic acids, allowing interaction with biomolecules and cells.
Surface-to-Volume Ratio	High. Beneficial for biological recognition and sensing.
Unique Properties	Often exhibit superparamagnetism or surface plasmon resonance at nanoscale.
Engineering Capability	Can be engineered to specifically target diseased cells. Properties (shape, size, surface charge) can be tailored.

2.1.1 Metallic Nanoparticles

Metallic nanoparticles are among the useful therapeutic approaches in managing AD via targeted drug delivery. This category includes gold, silver, selenium, iron, and cerium, all known for their promising anti-AD properties.

- **Gold Nanoparticles (Au-NPs):** Au-NPs are considered for AD therapy due to their transcytosis movement across brain endothelial cells without surface modification. These positively charged NPs can carry bioactive agents and facilitate targeted delivery to brain tissues. They possess optimal permeation properties across the BBB and exhibit neuroprotective qualities. Au-NPs conjugated with glutathione have demonstrated an anti-Alzheimer's effect by inhibiting Amyloid beta aggregation. When associated with anthocyanin, they show anti-amyloid beta aggregatory and anti-inflammatory properties, and their consumption can decrease acetylcholinesterase (AChE) levels. Light-activated AuNPs containing peptides have the potential to disintegrate preformed fibrils. Small AuNPs can effectively prevent beta amyloid accumulation and fibrillation by decelerating the nucleation mechanism. Larger AuNPs can accelerate beta

amyloid fibrillation, while smaller ones slow it down, and the latter show the highest inhibitory effectiveness. AuNPs have also been used in the development of AD biomarker biosensors due to their optical properties, chemical stability, electrical conductivity, biocompatibility, and catalytic activity. However, their overall negative charge might prevent them from passing across the BBB, and small AuNPs can severely compromise BBB integrity.

- **Superparamagnetic Iron Oxide Nanoparticles (SPIONs):** SPIONs conjugated with a beta amyloid-oligomer-specific scFv-AbW20 antibody and a class A scavenger receptor activator (XD4) have shown promising results in AD treatment. They also demonstrate exceptional early diagnostic potential for AD when combined with an beta amyloid-oligomer-specific antibody and a category A scavenger receptor activator. SPIONs are considered a safer alternative to gadolinium in MRI contrast agents and can be used at lower concentrations due to their higher effectiveness. They can be functionalized with desired motif sequences to achieve biocompatibility and solubility and are capable of targeting otherwise inaccessible brain areas due to their small size. IONPs have the potential to be developed as both T1 and T2 contrast agents. They can detect tau proteins in blood plasma when functionalized with anti-tau antibodies.

- **Selenium Nanoparticles (Se-NPs):** Se-NPs, and selenite NPs, have shown increased antioxidant effects and can potentially be used in neurodegenerative disorders like AD due to their essential micronutrient and antioxidant properties. Modified Se-NPs containing sialic acid have been found permeable to the BBB and inhibit beta amyloid accumulation reactions. Coating sialic acid, peptide-B6, and epigallocatechin-3-gallate (EGCG) with modified selenium NPs can also prevent beta amyloid aggregation due to high BBB permeability.

- **Cerium Nanoparticles (Ce-NPs):** Ce-NPs possess neuroprotective potential and antioxidant effects, quickly permeating the BBB with no neurotoxic effects. Ce-NPs coupled with triphenyl phosphonium (TPP) have shown anti-Alzheimer's effects and can prevent neuronal death.

- **Silica Nanoparticles (SiNPs):** SiNPs are used for BBB targeting due to their cellular uptake efficiency and localization in the cytoplasm. They can accumulate in intracellular amyloid cells and help treat AD SiNP scan decrease cellular apoptosis and reactive oxygen species (ROS) in a dose dependent manner. They have been studied for their efficiency in decreasing beta amyloid plaque formation and hyperphosphorylation. Intranasal silicon-coated NPs are also reported for effective brain targeting[7].

2.1.2 Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) or polymeric nanomaterials possess a wide variety of structures and morphologies, ranging in size from a few nano meters to over 1000 nm. Both natural and synthetic polymers can be used in their production, each yielding a unique set of characteristics. Polymeric NPs, due to their faster degradation and elimination from the body and lower toxicity risk, are more suitable for human therapeutic applications than inorganic NPs.

- **Poly (lactic-co-glycolic acid) (PLGA) Nanoparticles:** PLGA is a biodegradable polymer that hydrolyses into non-toxic endogenous metabolites like glycolic acid and lactic acid. PLGA provides targeted brain delivery and increased NP uptake. Surface functionalization of PLGA-NPs enhances their transport through the BBB, aiding in AD treatment. PLGA also improves drug safety against degradation and allows for alteration of in vivo and in vitro drug release profiles. Hydrophobic PLGA tends to be opsonized and eliminated by the reticuloendothelial system (RES), but coating with surfactant P-80 protects PLGA-NPs from clearance due to P-80's non-toxic, non-ionic, biodegradable, and hydrophilic nature.
    - **Curcumin-loaded PLGA-NPs:** Hydrophilic PLGA-coated curcumin NPs conjugated with Tet-1 peptide have shown antioxidative effects and demolished beta amyloid aggregates in an AD animal model.
    - **Vitamin D-loaded PLGA-NPs:** In murine AD models, vitamin D-loaded PLGA-NPs decreased neuronal apoptosis, reduced neuroinflammation, and increased cognitive function.
    - **Huperzine A-loaded PLGA-NPs:** Huperzine A loaded into PLGA conjugated with lactoferrin NPs demonstrated enhanced release kinetics and significantly decreased AD symptoms.
    - **Thymoquinone (TQ)-containing PLGA-NPs:** TQ, a bioactive component from *Nigella sativa* seeds, has shown promise in AD treatment. TQ-containing PLGA-NPs coated with polysorbate-80 (P-80) may be a viable and reliable method for delivering TQ to the brain across the BBB. TQ primarily reduces superoxide radicals by inhibiting xanthine-oxidase.
- **Polymer-based Nanoparticles (PBNPs):** Memantine-loaded PBNPs show anti-inflammatory and anti-Alzheimer's effects. Zinc and sitagliptin-loaded NPs have demonstrated improved cognitive dysfunction and reduced neuroinflammation.
    - **Chitosan Nanoparticles (CH-NPs):** Chitosan is a naturally derived cationic polysaccharide. CH-NPs are smaller than 70 nm, providing a greater surface-to-volume ratio. They have been shown to be effective in the intranasal

administration of FDA-approved AD medications like Rivastigmine. Chitosan can enhance medication penetration through the nasal mucosa by opening tight junctions. The surface charge of chitosan NPs can significantly influence beta amyloids aggregation, though the precise impact of positive and negative charges is debated. Nanoparticles for AD treatment should have a small positive surface charge to enhance blood circulation and reduce BBB toxicity [8].

2.1.3 Lipid-Based Nanoparticles (Liposomes, Solid Lipid Nanoparticles)

Lipid-based nanoparticles are a significant category of nanocarriers used in AD therapy.

- **Liposomes:** Liposomes consist of a phospholipid bilayer and are considered a highly probable solution for transporting medications across the BBB. They are composed of cholesterol and various phospholipids and range in size from approximately 20 nm to 1000 nm. Numerous surface modifications, such as coating with nutrients like glucose, have been implemented to boost liposomal carrier transport across the BBB, often facilitating transcytosis. Receptor-mediated transcytosis, often targeting the transferrin receptor (TFR13) and lactoferrin receptors (Lf15), is a common method for liposome delivery to the brain. Liposomes can be engineered to release drugs based on physiological changes like pH variations, enzyme activity, or glutathione levels.
    - **Curcumin-loaded Liposomes:** These can deliver drugs to the CNS, permeate the BBB, and exhibit anti-Alzheimer's effects.
    - **Osthole (Coumarin derivative) Liposomes:** These have shown increased intracellular uptake and cytoprotective effects, prolonging the cycle time and elevating Osthole accumulation in the brain.
    - **Donepezil (DPL)-loaded Liposomes:** Intranasal administration of DPL-loaded liposomes rapidly crosses the BBB, improves bioavailability, and reduces systemic toxicity.
    - **Rivastigmine-loaded Liposomes:** These can improve cognitive and behavioral development, reduce side effects, and increase drug concentration in the brain, leading to high therapeutic efficacy [9].
- **Solid Lipid Nanoparticles (SLNs):** SLNs are spherical nanocarriers with a solid lipid core matrix, preferred for drug delivery to penetrate the BBB due to their ability to solubilize lipophilic molecules. They are typically composed of monoglycerides, diglycerides, or triglycerides (e.g., tristearin), fatty acids, steroids, or waxes, stabilized with surfactants or emulsifiers to prevent agglomeration.

- **Donepezil (DPL)-loaded SLNs:** Intranasal administration of DPL-SLNs significantly increases drug concentration in the brain compared to intravenous or intranasal DPL solutions.
- **Curcumin-loaded SLNs:** These have been shown to reduce behavioral dysfunction and reverse several neurotransmitter imbalances in the brain of AD animal models.
- **Pomegranate extract-loaded Lipid Nanoparticles (LNPs):** These exhibited high antioxidant effects and decreased NFTs and beta amyloids deposition in an aluminum chloride-induced rat model of AD.
- **α-Bisabolol-loaded Cholesterol LNPs:** These prevent beta amyloids induced neurotoxicity and inhibit beta amyloids aggregation in nerve cells.
- **Erythropoietin (EPO)-encapsulated SLNs:** These overcome decreased BBB penetration due to EPO's hydrophilicity and high molecular weight, reducing oxidative stress and beta amyloids deposition while increasing spatial memory [10].

- **Nanostructured Lipid Carriers (NLCs):** NLCs consist of a disorganized inner lipid matrix of solid and liquid lipids, making them promising for targeted drug delivery. They can imitate the natural lipid environment of bio membranes, including the BBB. NLCs show high affinity to beta amyloids and promote its degradation. They are more stable and have good loading capacity than conventional dosages due to their lipophilic nature and smaller size, which facilitates drug molecule crossing of the BBB.
- **Curcumin-loaded NLCs:** These treat oxidative stress in AD, increasing curcumin bioavailability in the brain and reducing beta amyloids hallmarks.
- **Lipid Nanocapsules (LNCs):** Indomethacin (Ind)-loaded LNCs have been investigated for preventing beta amyloids induced cell damage and neuroinflammation.
- **Micro/Nano-emulsion-based Nanocarriers:** Microemulsions (MEs) can bypass the BBB via the nasal olfactory route, enabling quick drug absorption through highly vascularized mucosa, thus improving drug concentration in the brain and targeted delivery.
    - **Morin hydrate-loaded ME:** Intranasal delivery of morin hydrate-loaded ME is a potential strategy for AD treatment, overcoming issues of low solubility and poor bioavailability, and offering a non-invasive advantage.

- **Ibuprofen-loaded ME:** A novel ibuprofen-loaded ME showed significantly higher uptake in rat brains compared to intravenous or oral administrations.
- **Tacrine-loaded ME:** Intranasal administration of tacrine-loaded ME resulted in the quickest memory recovery in scopolamine-induced amnesic mice.
- **Huperzine A-loaded ME:** This improves cognitive function in mice compared to oral suspension.
- **Nano-emulsions (NEs):** These increase the efficacy of anti-AD drugs and targeted drug delivery. Naringenin nano-emulsions can overcome amyloid beta neurotoxicity and amyloid genesis. Memantine nano-emulsions administered intranasally cross the BBB and enhance the anti-AD effect. Donepezil hydrochloride nano-emulsions also show antioxidant and radical scavenging effects [11].

2.1.4 Carbon Nanomaterials (Quantum Dots, Nanotubes, Graphene)

Carbon nanomaterials, such as quantum dots, nanotubes, and graphene, are being explored for neurological applications.

- **Quantum Dots (QDs):** QDs offer unique properties that allow them to overcome limitations of conventional dyes and imaging techniques, enabling early detection of AD by tracking in vivo beta amyloids aggregation. Glycine-proline-glutamate (GPE)-coupled QDs (GQDG nanomaterial) inhibited A1-42 fibril aggregation, improved memory and learning in APP/PS1 transgenic mice, and can pass the MDCK cell monolayer due to their small size and high surface area. QDs can also electrochemically detect ApoE, an AD biomarker, with lower detection limits and greater accuracy for diluted human plasma.

2.1.5 Dendrimers

Dendrimers are highly branched polymeric materials with a central core, branches, and terminal functional groups, exhibiting a tree-like nanostructure. Their unique architecture allows them to effectively carry nucleic acids or encapsulated drugs due to their functional groups. They offer advantages such as high density, mono dispersity, controlled size, and a high degree of surface functioning, making them well-suited for site-specific drug administration.

- **PAMAM Dendrimers:** Poly amidoamine (PAMAM) dendrimers are widely used due to their high biocompatibility, flexibility, and low cost. PAMAM dendrimers combined with tacrine (an anti-AD medicine) improved therapeutic effectiveness and reduced toxicity. They have also been used for carbamazepine brain delivery to increase drug solubility, decrease dosage and frequency, and reduce side effects. Lactoferrin (Lf)-conjugated PAMAM dendrimers efficiently carried memantine to the brain, enhancing bioavailability and improving memory and behavioral function in an AD animal model [12]. Different types of nanoparticulate drug delivery system for Alzheimer's therapy are mentioned in the below fig-2.2

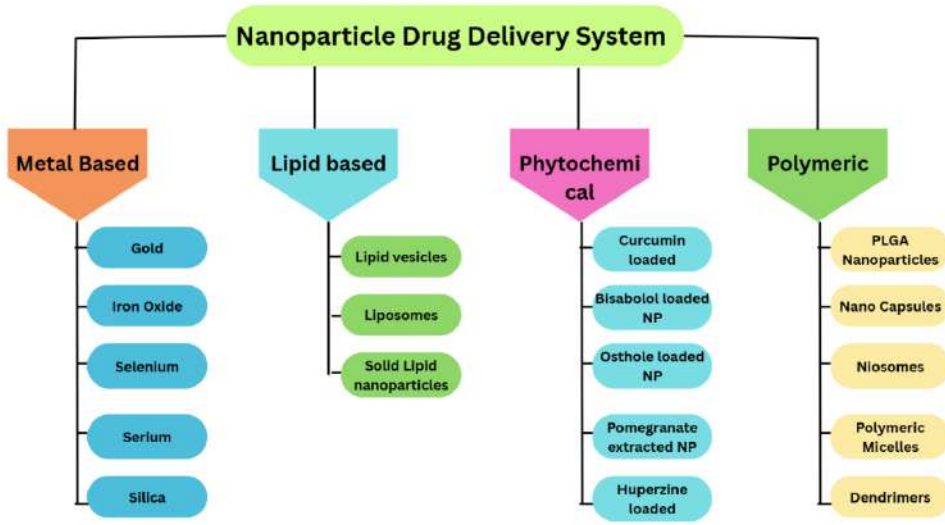

Figure 2.2: Different Types of Nanoparticulate Drug Delivery System for Alzheimer's Therapy

2.2 Nanoparticle Synthesis and Functionalization

Nanoparticle synthesis and functionalization are critical for tailoring their properties for specific neurological applications. NPs can be produced in different shapes (spherical, cubic, rod-like) and sizes to modify their movement across biological barriers. They can bind with a wide variety of desired ligands (by adsorbing, entrapping, or covalent bonding) to acquire new diagnostic, therapeutic, or physiological properties, including the ability to cross the BBB. For optimal therapeutic efficiency, NPs are ideally between 50 and 100 nm in size, spherical in shape, and possess a low positive or negative zeta potential. Coating NPs with polyethylene glycol (PEG) can attenuate protein adsorption in body fluids, increasing their blood half-life [13].

2.3 Challenges of Drug Delivery to the Brain: The Blood-Brain Barrier (BBB)

The blood-brain barrier (BBB) is a major physiological obstacle to drug delivery to the brain. It is a specialized part of the vascular system that stops bacteria, toxins, and other harmful substances from entering the brain. This physical interface between the central nervous system (CNS) and peripheral circulation obstructs molecular movement in the brain parenchyma. While a fantastic security system, it unfortunately prevents many drugs and substances from reaching the parts of the brain where they are needed in neurodegenerative diseases. The BBB restricts the movement of most therapeutic compounds, with only lipophilic molecules smaller than 400 Da able to cross. This presents a significant impediment to the development of novel CNS therapeutics. Different strategies and mechanisms for overcoming blood brain barrier is mentioned in the below table-3.

Table 2.3: Key Mechanisms for Nanoparticle BBB Penetration

Mechanism	Brief Description
Receptor-Mediated Transcytosis	Ligand binds to a specific transmembrane receptor, forming a vesicle that crosses the endothelial barrier.
Adsorptive-Mediated Transcytosis	Facilitates NP crossing of the BBB.
Ligand Functionalization	Attaching specific ligands to NP surfaces to improve BBB penetration (e.g., targeting BBB receptors, increasing hydrophobicity, improving circulation time).
Sink Mechanism	Anti-beta amyloid peptide antibodies on NPs remove soluble beta amyloids from brain into blood circulation.
Intranasal Administration	Bypasses the BBB by direct delivery to the brain via the nasal olfactory route.
Magnetic Guidance	External magnetic fields guide magnetic NPs to specific brain regions.

2.4 Strategies for BBB Penetration Using Nanotechnology

Nanotechnology provides new approaches to develop alternative drug delivery treatments for all stages of Alzheimer's disease. Nanomedicine aims to overcome BBB difficulties by providing effective drug delivery through targeted and controlled release with reduced adverse effects. NPs can overcome the BBB due to their high surface-to-volume ratio and long circulation times. They can achieve this through cellular absorption, modification with targeting groups, and transcellular lipophilic pathways. Different mechanisms of BBB transport are mentioned in below fig-3.3

- **Receptor-Mediated Transcytosis:** This is a highly successful and often used method for NP delivery to the brain. Macromolecular ligands such as proteins, hormones, enzymes, and growth factors are transported to the brain through this process, where the ligand binds to a specific transmembrane receptor, the membrane invaginates, and the receptor-ligand complex forms a vesicle that is transported across the endothelial barrier.
- **Adsorptive-Mediated Transcytosis:** This mechanism also facilitates NP crossing of the BBB.
- **Ligand Functionalization:** The physicochemical properties of NPs are modified by attaching different ligands to their surface to facilitate drug delivery. Examples of ligands that facilitate BBB penetration include those that interact with BBB receptors (e.g., transferrin or insulin receptor, glucose transporter), those that increase NP charge and hydrophobicity (e.g., amphiphilic peptides), and those that improve blood circulation time (e.g., PEG or PEG-PLGA).
- **Sink Mechanism:** This involves loading NPs with anti-beta amyloids peptide antibodies that initiate a "sink mechanism," removing soluble beta amyloids peptides from the brain into the blood circulation.
- **Intranasal Administration:** This route can bypass the BBB and deliver drugs directly to the brain via the nasal olfactory route.
- **Magnetic Guidance:** Magnetic nanoparticles can be guided by external magnetic fields to target specific brain regions [14].

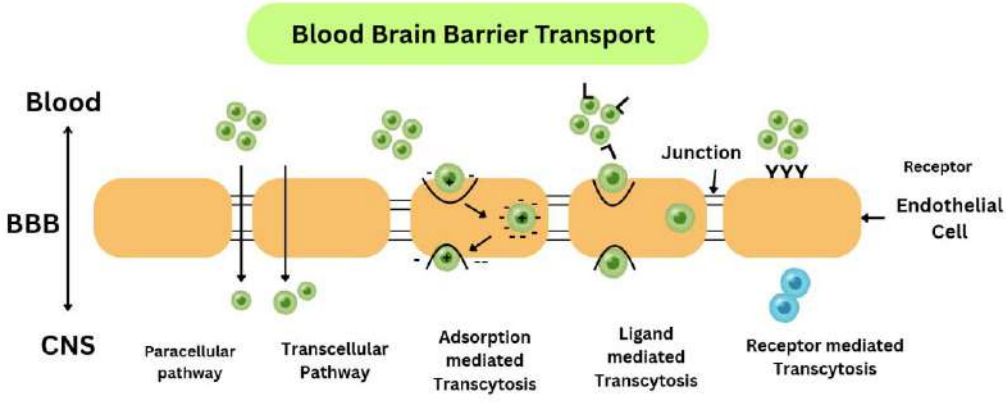

Figure 2.3: Different Types of Mechanisms for BBB Transport.

3. Nanotechnology-Enabled Diagnostics for Alzheimer's Disease

Nanotechnology is revolutionizing the early detection and imaging of AD by providing nanoscale technologies with unprecedented capabilities to identify the disease. Nano sensors and nanoparticles, including quantum dots, enhance the sensitivity of diagnostic tools to detect biomarkers at low concentrations. Nanotechnology offers significant potential in diagnosing neurological disorders like AD.

3.1 Early Detection of Biomarkers

Nanotechnology offers highly efficient signal transduction methods for the early detection of AD biomarkers.

3.1.1 Amyloid-Beta Detection

Nanotechnology-based approaches have largely focused on preventing beta amyloids from aggregating or sequestering the peptide to reduce its brain level, known as the "sink effect".

- **Nano biosensors:** Quantum dots can be used to electrochemically detect ApoE, an AD biomarker, with high sensitivity in diluted human plasma.
- **Imaging Probes:** Fluorescent quantum dot probes conjugated with an anti- beta amyloids antibody have been used for molecular imaging of beta amyloids aggregation in mouse models of AD. In transgenic mice, fluorescence intensity was lower in beta amyloids fluorescent mice compared to APP transgenic animals in the hippocampus, cerebral cortex, sagittal septum, and striatum.

3.1.2 Tau Protein Detection

Tau protein aggregation is a defining characteristic of AD, leading to the formation of neurofibrillary tangles that disrupt neural communication and ultimately result in cognitive decline. Nanotechnology has emerged as a revolutionary tool in addressing the pathological accumulation of tau protein.

- **Magnetic Nanoparticles:** Iron oxide nanoparticles functionalized with anti-tau antibodies can identify tau proteins in the blood plasma of AD patients.
- **Theranostic Nanocomposites:** Multifunctional nanocomposites have been designed to monitor methylene blue release (a tau aggregation inhibitor) through its up-conversion fluorescence, offering insights into its content in the lesion area. This material effectively mitigates cytotoxicity from beta amyloids and tau aggregation.

3.1.3 Neuroinflammation Markers

Current strategies for developing AD therapies include managing neuroinflammation, which involves increased release of cytotoxic hydrogen peroxide.

3.2 Nano bio sensors and Imaging Probes

Nanotechnology offers accurate imaging of neural tissues for early diagnosis and personalized therapy. NPs can be integrated with specific biomarkers to detect certain histological phenotypes via ultrasound and measure biomarkers.

3.2.1 Quantum Dots for Bioimaging

Quantum dots offer unique properties that overcome the limitations of conventional dyes and imaging techniques, enabling early detection of AD by tracking in vivo beta amyloids aggregation in mice.

3.2.2 Magnetic Nanoparticles for MRI Enhancement

Magnetic nanoparticles facilitate nebular repair and neuromodulation. They are considered a safer alternative to gadolinium in MRI contrast agents and can achieve similar relaxation changes at lower concentrations. Magnetic nanoparticles can be dual functionalized with amyloid-binding dyes and antioxidants to aggregate with Aβ plaques and relieve memory impairments in AD transgenic mice. MRI of mouse brains has successfully detected these magnetic nanoparticles and plaques.

3.2.3 Gold Nanoparticles for Biosensing

Gold nanoparticles are frequently used in the development of AD biomarker biosensors due to their optical characteristics, chemical stability, electrical conductivity, biocompatibility, and catalytic activity. They can be combined with antibodies to identify beta amyloids proteins, increasing signal and improving electron transfer efficiency.

3.3 Liquid Biopsy Approaches Using Nanotechnology

Early diagnosis of AD can be achieved through liquid biopsy approaches. Immuno sensing utilizing liposomes encapsulated with beta amyloids peptide and attached to a screen-printed carbon electrode has shown the ability to distinguish plasma and CSF samples from AD patients. This approach is a first step towards successful diagnosis of AD in the preclinical stage using plasma samples [15].

4. Nanotechnology-Based Therapeutic Strategies for Alzheimer's Disease

Nanomedicine provides a new, alternative pathway for the development of AD treatment interventions. It has shown significant potential in improving drug delivery, diagnosis, and tissue repair in various neurological disorders.

4.1 Targeted Drug Delivery to the Brain

Drug delivery to the brain is one of the most challenging parts of treating neurological disorders. The blood-brain barrier (BBB) is a major physiological obstacle that nanotechnology aims to overcome. Nanocarriers, including liposomes and polymeric carriers, facilitate targeted drug delivery across the BBB to specific regions of the brain.

4.1.1 Enhancing Bioavailability and Reducing Systemic Toxicity

Nanotechnology-based strategies can improve the bioavailability and specificity of drug targeting in the brain. Nanocarriers have numerous advantages over conventional treatments, such as bypassing hepatic metabolism, reducing dosage, enhancing drug stability and bioavailability, and enabling targeted delivery at the site of action. This results in a reduction in the number of adverse effects experienced by patients.

- **Donepezil-loaded SLNs:** Intranasal administration of Donepezil-loaded solid lipid nanoparticles (SLNs) significantly increases the drug concentration in the brain compared to intravenous or intranasal solutions, and scintigraphy studies confirmed localization in the rabbit brain.
- **Nanostructured Lipid Carriers (NLCs):** NLCs protect active drugs from enzyme degradation, allowing them to reach the target site.
- **PLGA Nanoparticles:** PLGA nanoparticles enhance drug safety against degradation and allow for manipulation of in vivo and in vitro release profiles. Polysorbate-80 (P-80) coating on PLGA-NPs shields them from opsonization and clearance by the body, prolonging their circulation time [16].

4.1.2 Overcoming Multi-Drug Resistance

Nanomaterials are capable of delivering multiple drugs (e.g., chemical compounds, genes, peptides, and antibodies) at once, suggesting a future use in multi-target combination therapies for AD. This approach aims to address the complexity of AD pathophysiology, which involves multiple pathogenic factors and targets.

4.2 Clearance of Amyloid-Beta Plaques and Tau Tangles

The current consensus in AD research is that, compared to hyperphosphorylated tau and beta amyloids oligomers. Beta amyloids plaques and neurofibrillary tangles (NFTs) have a smaller contribution to memory impairment. However, clearance of these pathological aggregates remains a critical objective in AD treatment.

4.2.1 Nanoparticle-Mediated Beta Amyloids Disaggregation

Nanoparticles can facilitate the clearance of beta amyloids plaques and tau tangles.

- **Nanoparticle-mediated Beta Amyloids Disaggregation:** Nanoparticles, particularly gold nanoparticles, can effectively inhibit protein aggregation. Light-activated gold nanoparticles containing peptides can cause the disintegration of preformed beta amyloids fibrils. Smaller gold nanoparticles can prevent beta amyloids aggregation and fibrillation by decelerating the nucleation mechanism.

- **Dual-functional Nanoparticles:** Self-destructive nano sweepers from peptide-polymers can capture beta amyloids and promote its degradation by stimulating autophagy, leading to decreased soluble and insoluble beta amyloids levels in the brain.

- **Selenium Nanoparticles:** Selenium nanoparticles modified with sialic acid can inhibit beta amyloids accumulation.

- **Curcumin-loaded Nanomaterials:** Curcumin-loaded PLGA nanospheres with selenium nanoparticles showed potent inhibitory impacts against beta amyloids aggregation in a transgenic AD mouse model. Curcumin-loaded chitosan and bovine serum albumin nanoparticles have also been shown to boost drug penetration and speed the phagocytosis of beta amyloids peptide.

4.2.2 Enzyme-Loaded Nanoparticles for Beta Amyloids Degradation

Enzyme-loaded nanoparticles can contribute to the degradation of beta amyloids

- **CRISPR-Cas9 Amphiphilic Nanocomplexes:** These can significantly decrease BACE1 expression, leading to reduced production of APP β-cleavage products and amyloid β plaque formation.

4.2.3 Immunotherapy Approaches Using Nanocarriers

Nanotechnology offers an effective alternative to traditional immunotherapy for locating and dissolving protein aggregates in brain cells by applying nanoparticles coated with antibodies directed against specific target proteins.

- **Antibody-functionalized Polymer Nanoparticles:** These can lead to memory recovery in AD-like transgenic mouse models by reducing beta amyloids soluble peptides.

- **Superparamagnetic Iron Oxide Nanoparticles (SPIONs) with Antibodies:** SPIONs conjugated with beta amyloids oligomer-specific scFv-AbW20 antibody have shown therapeutic potential for AD.

- **Nano vehicles with Chitosan and Beta Amyloids Fragments:** These have been used to target amyloid-containing cells in AD, and contrast agents like

fluorescein isothiocyanate (FITC) and Alexa Fluor enhance NP-beta amyloid absorption across the BBB [16].

4.3 Neuroprotection and Neurogenesis

Nanotechnology contributes to neuroprotection and neurogenesis in AD by delivering various beneficial agents.

4.3.1 Delivery of Neurotrophic Factors

Nanocarriers can deliver neurotrophic factors to support neuronal survival and function.

- **Erythropoietin (EPO)-encapsulated SLNs:** These overcome the limited BBB permeation of EPO, decreasing oxidative stress and beta amyloids deposition while increasing spatial memory in AD models.
- **Bone Morphogenetic Protein-9 (BMP-9) Derived Peptides:** Chitosan nanoparticle-based methods have been used to deliver SpBMP-9, a peptide that stimulates cholinergic neuron development and inhibits beta amyloids.

4.3.2 Antioxidant Nanoparticles

Antioxidant nanoparticles help combat oxidative stress, a multifactorial contributor to AD pathogenesis.

- **Selenium Nanoparticles (Se-NPs):** Se-NPs possess antioxidant properties that can help prevent cellular damage from reactive oxygen species (ROS).
- **Curcumin Nanoparticles:** Curcumin is an antioxidant with low toxicity and a free radical scavenger. Its nanocarrier delivery can enhance bioavailability and provide sustained brain exposure to treat AD symptoms.
- **Resveratrol-loaded Mesoporous Nano-selenium Delivery System:** This system showed anti-oxidative and anti-inflammatory effects, inhibiting beta amyloids aggregation and reducing tau hyperphosphorylation.

4.3.3 Anti-inflammatory Strategies

Nanotechnology-based approaches can attenuate chronic neuroinflammation in AD.

- **PPaRy agonist-loaded PLGA-PEG NPs:** These can modulate inflammatory responses and reduce beta amyloids plaque formation.
- **Berberine-loaded Multiwalled Carbon Nanotubes:** These inhibit brain oxidative damage induced by beta amyloids.
- **Quercetin Nanoparticles:** Quercetin, an antioxidant, can attenuate inflammation and reduce oxidative stress-related neuronal death [10, 11, 17].

4.4 Gene Therapy and CRISPR-Cas9 Delivery via Nanocarriers

Gene therapy for AD aims to maintain therapeutic expression levels of selected genes long-term, altering or activating proteins involved in neurodegenerative processes for neuroprotection and neuro restoration. Nanocarriers are crucial for overcoming the poor bioavailability of nucleic acid drugs due to enzymatic degradation and immune clearance.

- **CRISPR-Cas9 Amphiphilic Nanocomplexes:** These can deliver CRISPR-Cas9 to hippocampal brain regions to attenuate memory impairment. In vivo neuronal gene editing via CRISPR-Cas9 amphiphilic nanocomplexes has alleviated deficits in mouse models of AD.
- **siRNA-encapsulating Nanomedicines:** Gene drugs like LRsGAR, encapsulating siGSK-3 beta, can downregulate GSK3 beta expression, reducing p-Tau accumulation.
- **Dendrimers for Gene Delivery:** Dendrimers can carry DNA into the nucleus by endocytosis, enabling transcription into the appropriate gene and product, and do not stimulate the immune system [18,19].

4.5 Cell-Based Therapies Enhanced by Nanotechnology

Nanotechnology can enhance cell-based therapies for AD. For example, mesenchymal stem cells (MSCs) and neural stem cells (NSCs) are being explored, and nanoparticles can promote their targeted delivery and engraftment. Nanotechnology can also enhance the delivery and differentiation of stem cells for regenerative therapies in AD [20].

5. Emerging Trends and Future Directions

Nanotechnology is poised to revolutionize AD research and treatment, offering new solutions for diagnosis, therapy, and prevention of this debilitating disease. Future trends in nanomedicine for neurology emphasize precise treatments, early detection methods, and personalized medicines.

5.1 Theranostic Nanoplatforms for AD (Diagnosis and Therapy)

Theranostics is an emerging field that combines diagnostic and therapeutic functionalities within a single platform. Researchers are developing nanoparticles that perform both diagnostic and therapeutic functions simultaneously, enabling real-time monitoring of treatment development. This integration allows for a more precise and dynamic approach to AD management, where diagnosis informs therapy, and therapy can be adjusted based on real-time feedback [21, 22].

5.2 Personalized Nanomedicine for AD

Personalized nanomedicine for AD focuses on tailoring therapies to the unique genetic, molecular, and biological makeup of individual patients. Nanotechnology, combined with genomics and artificial intelligence, provides a platform for creating personalized treatment strategies. This approach aims to deliver more precise drug delivery and enhance therapeutic effectiveness by considering individual patient profiles.

5.3 Artificial Intelligence and Machine Learning in Nanomedicine Design

The convergence of nanomedicine with artificial intelligence (AI) and machine learning (ML) promises significant advancements in tailored neurological treatments. AI algorithms can be combined with nano sensors for real-time monitoring of AD biomarkers, providing valuable insights into disease progression and response to treatment. This integration can also facilitate the design of personalized nanomedicines, customized to an individual's genetic profile.

5.4 Bio fabrication and Nanorobotics for Neurological Repair

While not extensively detailed for AD in the provided texts, nanotechnology generally offers potential for tissue repair in neurological disorders. Nano structural scaffolds can facilitate neural regeneration, assisting recovery associated with neurotrauma. The broader field of bio fabrication and nanorobotics could contribute to future neurological repair strategies, potentially offering sophisticated methods for targeted cellular repair and regeneration within the brain [23,24].

6. Challenges and Ethical Considerations

Despite its immense promise, the clinical translation of nanomedicine in neurology faces several significant challenges, including issues of biocompatibility, safety, and regulatory approval.

6.1 Nanotoxicity and Biocompatibility Issues

Nanotoxicity is a major concern for nanomedicines, as nanoparticles can more easily cross the BBB than larger molecular drugs, raising concerns about potential toxicity. While preclinical studies demonstrate significant improvements in AD models, their clinical translation is somewhat lacking due to the need to demonstrate safety.

- **Immuno toxic Responses:** Nanoparticle constituents, such as nucleic acids, antibody fragments, peptides, and proteins, can trigger immune toxic responses.
- **Chronic Toxicity:** Identifying acute nanoparticle toxicity is possible in clinical experiments, but assessing potential chronic toxicity from prolonged exposure and accumulation in living organisms is still largely unexplored.

- **Inefficient Clearance and Accumulation:** Some nanoparticles may not be efficiently eliminated by clearance systems, leading to brain accumulation and cytotoxicity, potentially causing injuries from prolonged presence.
- **Biocompatibility:** Nanomaterials must be non-toxic and well-tolerated by human tissues, without triggering inflammatory responses or immune system dysregulation. The potential for DNA damage or mutations, particularly toxicity to neurons and other brain tissues, must be minimized [25].

6.2 Regulatory Pathways for Nanomedicines

The regulatory landscape for nanomedicines is complex and poses significant challenges. Regulatory agencies, such as the FDA, find it difficult to establish guidelines for nanoparticle-based therapies due to their unique properties and complexity. This adds more problems and requires more time for clinical application of these therapies for neurological disorders. Clear guidelines and regulations are essential to ensure the safe and ethical development and utilization of these technologies.

6.3 Scaling Up Production and Commercialization

The production of nanoparticles is a complex and costly process, requiring specific ingredients, instruments, and optimal conditions, especially for multifunctional nanoparticles with preventive and therapeutic roles. Further experimental studies are crucial to reduce the clinical application costs of nanotechnology in medical care [26,27].

Conclusion

Nanotechnology offers innovative approaches to overcome the limitations of conventional AD therapies, particularly in targeted drug delivery across the blood-brain barrier (BBB) and early disease detection. Key advancements include the development of various nanocarrier types such as metallic nanoparticles, polymeric nanoparticles, lipid-based nanoparticles (liposomes, solid lipid nanoparticles, nanostructured lipid carriers), carbon nanomaterials (quantum dots), and dendrimers. These nanocarriers can be engineered to enhance drug bioavailability, reduce systemic toxicity, and facilitate the clearance of beta amyloids plaques and tau tangles. Nanotechnology also plays a crucial role in improving neuroprotection, neurogenesis, and enabling gene therapy and cell-based therapies. Furthermore, nanodiagnostics are redefining early detection through highly sensitive biomarker identification and advanced imaging techniques.

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Conflicts of Interest

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