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# Translational Pharmacology Of Nucleic Acid And Peptide Nanotheranostics For Precision Alzheimer's Disease Management

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## ABSTRACT

Alzheimer's disease (AD) is a chronic and progressive neurodegenerative disorder characterized by extracellular amyloid-β (Aβ) plaque deposition and intracellular neurofibrillary tangles formed by hyperphosphorylated tau protein. These pathological hallmarks drive synaptic dysfunction, neuroinflammation, neuronal loss, and cognitive decline. Current pharmacological therapies primarily provide symptomatic benefit and fail to modify the underlying disease process, highlighting the urgent need for disease-modifying anti-Alzheimer's disease (DMAD) strategies. Therapeutic approaches aimed at inhibiting the aggregation of Aβ and tau or enhancing their clearance remain the most validated disease-targeted interventions. Despite decades of research, small-molecule agents have demonstrated limited clinical efficacy in addressing these complex pathological mechanisms. In contrast, the approval of aducanumab, an amyloid-β–targeting monoclonal antibody, has transformed the therapeutic landscape by establishing biological macromolecules as viable DMAD candidates. This milestone has accelerated pharmacological research into nucleic acid- and peptide-based therapeutics, including microRNAs, small interfering RNAs, antisense oligonucleotides, aptamers, and antibodies, which offer enhanced target specificity and mechanistic precision.

**Keywords:** Nucleic acids, Nanotechnology, siRNA, miRNA, Pathology, DMAD, Alzheimer's Disease.

## 1. Introduction

Alzheimer's disease (AD) is a leading progressive neurodegenerative condition affecting the aged population across the globe. It is incurable, with only a handful of symptomatic management options. AD, the most prevalent form of dementia in the aging population, has affected nearly 50 million people globally and is anticipated to reach the 150 million mark by 2050 due to improved medical technologies helping to

increase life expectancies (Gaudreault and Mousseau, 2019). Therefore, it has become a global health crisis due to this alarming rate of disease occurrence. Even after the identification of the pathological hallmarks and pathways participating in AD progression, after decades of research, we are unable to cure the disease. The researchers are trying to identify early-stage diagnostic markers for AD, which generally goes undiagnosed for ~20 years after its initiation. Similarly, focus is being laid on developing theranostic tools for inhibiting the disease at earlier stages and to be used for a personalized care. In this process, the pathological hypothesis that initially revolved around senile plaques and neurofibrillary tangles (NFT) has evolved to cholinergic system, neuroinflammation, and oxidative stress cascades, as these processes prominently participate far before the peptide aggregation (Cao and Zhang, 2022).

Small molecules have been designed and formulated for AD management as they offered a better pharmacokinetic profile, biological membrane permeability, and ease in synthesis and formulation (Makurvet, 2021). Although they come with their own set of challenges due to the multifactorial nature of the disease pathology and complications arising due to peripheral toxicity and untargeted effects of these drugs after reaching systemic circulation. On the other hand, nucleic acids and peptides can mimic the biological system and act at undruggable targets through mRNA expression alteration. Another major disadvantage of small molecules is a limited effect duration, which demands higher frequency of drug administration. This problem is also resolved by biological macromolecules as they can act at the genetic level multiple times (M. Liu et al., 2025).

Nucleic acid and other biological macromolecules have a limitation, due to their large molecular size, that they cannot pass through biological barriers like cell membrane and BBB. In such scenarios, nanotechnology which was used for targeting small molecules has been applied to macromolecule research. Integrating nanotechnology and macromolecule therapy might prove to be an excellent theranostic approach for AD management. It has become an important tool for personalized and targeted disease management. Nanoparticles were earlier used only as a carrier, but recent advances has shown a trend of using these nanoparticles not just as vehicle, but also used for diagnosis and treatment purposes, generating a synergistic action on AD management (Miao et al., 2024). In this review, we provide the current landscape for the application of nanotechnology, nucleic acid, and peptide in AD theranostic, which has not been previously covered in a unified perspective. We briefly discussed the methods and polymers widely used for the AD theranostic application. We focused on highlighting the trends in the drug delivery aspect for these agents through a nanotechnological approach. The challenges faced by these modalities for their clinical translation and synergistic potential in the AD theranostic revolution have been discussed further.

## 2. Pathological advances involved in AD

Neurodegenerative conditions like Alzheimer's and Parkinson's are pathologically complex diseases with multiple factors contributing to their progression. As is well known, amyloid senile plaques and tau hyperphosphorylation are the cores of AD pathology; besides this cholinergic system also plays an important role in the pathological progression. Recently, scientists have tried to group the pathology not based on the pathological hallmarks (i.e., tau and Aβ) but have tried to focus more on the pathological processes leading to aggregate formation. It includes oxidative stress and neuroinflammatory hypothesis.

The amyloid hypothesis was formulated in the 1980s, and since then, it has been considered the most reliable AD pathogenesis mechanism. According to this hypothesis, either overproduction or improper clearance of insoluble Aβ leads to the accumulation of senile plaques in different regions of the brain, which otherwise are being cleared due to their soluble nature. Amyloid precursor protein (APP) is responsible for the production of Aβ and participates in neuronal functions like neural growth, maturation, and migration at different brain development stages. The APP protein is cleaved by two transmembrane enzymes, namely β-secretase and γ-secretase, where the former cleaves APP within the lipid bilayer, generating soluble APP-β and β-C-terminal fragment 99. The C-terminal fragment is further cleaved by γ-secretase to produce Aβ and AICD50. The produced Aβ is of varying length, where the 40 amino acid length is produced more (~90%), while the 42 amino acid form is more toxic due to its higher aggregation tendency. These peptides

self-assemble into oligomers and plaques. Accumulation of these triggers an immune reaction and inflammation, which further leads to neurotoxic cascade activation, neurodegeneration, and cell death. They also interfere with the synaptic function, hindering cellular communications (Zhang et al., 2024).

Tau is an axonal protein widely distributed throughout the brain. This microtubule-associated protein is responsible for microtubule assembly, protein synthesis, neuroprotection, apoptosis, and nutrient transport. The protein is soluble in its innate form, but in pathological conditions, it becomes hyperphosphorylated, leading to its misfolding and aggregation as neurofibrillary tangles (NFT), which is another pathological hallmark of AD. Both proteins act synergistically in the neurodegenerative pathological cascade of AD (Shakir and Dugger, 2022). The cholinergic hypothesis is based on the reduced acetylcholine (ACh) production, which is of prime importance for the proper functioning of the cerebral cortex and hippocampus associated with memory and cognitive activity of the brain. These activities are most adversely impacted in AD as the ACh-mediated regulation of neurotransmission and long-term potentiation is impaired in the pathological state (Ju and Tam, 2022).

Neuroinflammation has started to evolve as the pathological hub for neurodegenerative conditions like AD, PD, and amyotrophic lateral sclerosis. The action is mediated by the glial cells of the brain, which are the resident immune cells in the brain, namely, astrocytes and microglia. In the initial cellular insult, the innate immune response from these cells is protective towards the cell. The immune reaction tries to attack the pathological insult using inflammatory mediators, but upon repeated stimuli, the protective cascade turns to a pathological one. Microglia and astrocytes both get predominantly activated to their proinflammatory M1 and A1 subtypes, respectively. This leads to inflammatory mediators like IL-1β, TNF-α, IL-6, and IL-18 overproduction, while the anti-inflammatory proteins like IL-4 and IL-10 are suppressed, which are responsible for activation of anti-inflammatory phenotypic conversion for microglia (M2) and astrocytes (A2). Hence, an aggravated inflammatory cascade is observed in the AD pathological cascade (Deture and Dickson, 2019). Similar to inflammatory markers, oxidative stress also leads to an activated inflammatory cascade. Reactive oxygen species (ROS) play a significant role in disrupting the oxidant-antioxidant homeostasis in the brain. In pathological conditions, antioxidant enzymes like catalase, glutathione reductase, superoxide dismutase, and glutathione are reduced while the oxidative stressors like lipid peroxides, superoxides, free radicals, etc. are increased tremendously. Hence, oxidative damage and neuroinflammation is being targeted together in the evolving therapeutic avenue (Tang et al., 2023).

## 3. **Barriers between CNS and PNS**

The brain is a structurally and functionally sophisticated and most complex organ of the body, which is made of nearly 100 billion neurons protected by glial cells and meninges. The brain is structurally protected from the rest of the physiological systems, mainly by the blood-brain barrier. But BBB isn't the lone hindrance for drug-delivery to the brain, as the cerebrospinal fluid barriers with blood, glymphatic system, and meninges are also contributing to affecting the pharmacokinetics and pharmacodynamics of the drug targeted for the brain. The brain capillary endothelial cells surrounding the blood capillaries across the brain are the largest interface for molecular exchange. They have a limited number of pores and higher glycocalyx content than other vessels, creating an extremely tight junction of the BBB. Surrounding the brain capillary endothelial cells are the basement membrane, comprising astrocytes and pericytes. This membrane is the key permeation factor in the BBB. After the basement membrane there is the tight junction. They create a high-resistance electrical barrier due to their protein composition (claudin, occluding, and junction adhesion molecules), rendering their cell adhesion and tight gap properties (Brookes et al., 2022; Profaci et al., 2020). The physicochemical properties of the drug will also decide its transport mechanism, besides the physical barrier, e.g., hydrophobic drugs can be absorbed through transcellular absorption. In contrast, hydrophilic drugs need paracellular diffusion (also limited due to tight-junction permeation) or through transcellular receptor-mediated transport. This is further complicated by the presence of efflux pumps, transport receptors, and enzymes (Laksitorini et al., 2014). The P-glycoprotein (P-gp) is present on the brain endothelial cells of BBB which is responsible for export and inefficient residence of drug inside the cell.

The LDLR (low-density lipoprotein receptor) is the key regulator of transcytosis through the BBB. The LDLR is a useful target for targeting the BBB, where LDLR-related protein 1 (LRP-1) is widely explored. LRP-1 strictly regulates the tight junction proteins (Zhao et al., 2016).
In pathological conditions like AD, the integrity of the BBB is lost, also losing its properties and homeostasis. Aβ-mediated synaptic dysfunction of BBB is an important pathological hallmark, which is also explored as an early diagnostic marker for AD. The disrupted BBB homeostasis is exploited as an enhanced drug delivery opportunity, but the unpredictable and non-uniform pattern of BBB damage stands as a major challenge. Mannitol is used for reversible BBB disruption which would enhance the drug permeability to the brain. The tight junction assembly is also interrupted using RNA interference technique (Barchet and Amiji, 2009). Therefore, understanding the molecular interaction between the BBB components and the therapeutic agents becomes very important (Brookes et al., 2022).
Drug delivery enhancement to the brain uses several invasive and non-invasive techniques. The invasive techniques use surgical procedures to deliver the drug through implants (e.g., biodegradable wafers) or cannulas or direct transcranial injections. The major limitation of implants as a delivery system is the precise implantation near the site of action because as this distance increases, the effective drug concentration decreases exponentially. Nanocarriers (e.g., apoferritin cage system) and convection-enhanced delivery of drugs have also been explored for CNS drug delivery. The non-invasive options would be more preferable for AD-like chronic and progressive disease, especially for the ageing population (patient compliance), including oral formulation and nasal formulation as the most efficient routes. The transcellular route of drug absorption becomes more difficult due to BBB in brain and to overcome this challenge and enhance transcellular drug absorption in brain, cyclic peptide prodrug method was utilized (Paul et al., 2018). The technique nicks the peptide ends chemically to enhance its stability and prevent enzymatic degradation by metabolic enzymes, mimicking physiological proteins. This forms a safe delivery system for the active drug loaded as a prodrug into such a system (Huo et al., 2019). Scientists have also tried to deliver drugs to the brain using the nose-to-brain delivery, oral lipid-based drug delivery, and the intestinal mucosa-mediated delivery (Koduru et al., 2023). Viral vectors are also experimented with for gene therapy in neurological conditions by transfecting their genotype into the target site. Exosomes is still an evolving avenue for drug-delivery to the brain, but it has been widely explored for nucleic acid, macromolecules, and peptides delivery (Haqqani et al., 2013; Yang et al., 2017). The delivery systems used for BBB permeation are discussed in detail in later sections.

## 4. Methods for Brain Targeting

For any kind of drug, either small molecule or biological macromolecule, the first barrier that has to be faced by every entity is the cell membrane, which acts as the primary barrier in cells. In neurological conditions, targeting the brain is the ultimate aim, for which, besides the cell barrier, the drug has to pass through the other physiological barriers, like the BBB. Lipophilic compounds with molecular weight <500 Da can permeate through the cell membrane and BBB, but therapeutic macromolecules like peptides and nucleic acids don't fall in this category. In such a scenario, nanotechnology and receptor-mediated uptake are the only avenues for efficient delivery to the brain. Receptors like transferrin, insulin-like growth factor 1, leptin, insulin, and LRP1 are principally active and targeted for designing such delivery systems (Kanwar et al., 2012).

Besides this mechanism, several peptides have the potential to penetrate the bilayer lipid membrane of the cells and even permeate through the meninges and the BBB. These cell-penetrating peptides either act through receptor targeting or may facilitate the transcytosis kind of cellular mechanism. These peptides generally have 8-30 amino acid residues, which can be further modified for therapeutic targeting (Heitz et al., 2009). The introduction of nucleic acids and peptides directly to the cerebrospinal fluid through intracerebroventricular infusion also appears to be a promising approach. The main advantage of this method is that it directly delivers the drug to the brain, escaping any physiological barrier, avoiding any adverse event due to organ accumulation, and in a safe therapeutic window due to lower dosage requirement. The CSF turnover rate, being nearly 4-5 hours, ensures proper delivery of the drug to the

blood. Being invasive is the major drawback of this technique. As AD affects the aged population majorly, other health complications and underlying conditions may further reduce the application of this technique to clinical cases. Although in preclinical studies it is widely used and has shown promising effects, the clinical application remains limited (Pardridge, 2007). Alternatively, the nasal route became an important aid in brain targeting, where parenteral and oral administration applications are limited. It is a non-invasive method directly targeting the brain through trigeminal and olfactory nerves for drug delivery. Several formulations, like microemulsions, in-situ gels, nasal powders, inserts, and nano-carrier-based formulations, have been studied for the same purpose (Jülke and Beck-Sickinger, 2025; Papakyriakopoulou and Valsami, 2025).

## 5. Role of Nanotechnology in AD Theranostic

Oral delivery of the drugs is the most convenient route of administration for chronic disease management. But the systemic metabolism and physiological barrier between systemic circulation and the brain limit its application for neurodegenerative conditions like AD. Playing around with the physicochemical properties of the therapeutic agent also affects its efficacy and toxicity window. Due to the BBB constraint, nanotechnology has gained enormous attention in delivering therapeutic agents to the brain. Engineered biocompatible and biodegradable nanoparticles can cross the BBB and are easily surface manipulated to achieve desired properties for the drug and the delivery system. These nanoparticulate systems comprise an encapsulation unit and a nano-engineered complex unit. The encapsulation unit aids in drug protection. The nanoengineered complex, on the other hand, is designed to be responsive to various physiological conditions like enzymes, pH, or temperature, depending on the polymer's nature, which ensures targeted drug delivery at a desired rate (Mota et al., 2023). Various types of nanoparticle systems have been developed as delivery vehicles for the therapeutic agents like polymeric nanoparticles, liposomes, niosomes, exosomes-like liposomes, dendrimers, solid lipid nanoparticles, micelles, nanoemulsion, etc. meant for different routes of administration.

Polymeric nanoparticle system (PNP) is made up of a biocompatible and biodegradable colloidal polymeric mixture using hydrophobic, electrostatic, or hydrogen bond interactions between polymer and drugs. In such a system, the hydrophobic drug is enclosed within a densely arranged polymeric matrix, providing a steric stability to the nanoparticles. The drug can either be directly encapsulated, engrossed, or chemically linked to the polymer for delivery. Brain targeting polymers used for such a system include chitosan, lactide-co-glycolic, poly-allylyamine hydrochloride, poly-ethylene imine, etc. Rivastigmine PNP showed improved bioavailability of the drug when formulated as a transdermal film (Ravi and Vishal Gupta, 2019). Donepezil-loaded PLGA nanoparticles were embedded into PVA/PEG nanofibers generated for sublingual administration. The formulation showed ultra-fast release profile for the formulation (~2s disintegration time) while the donepezil release profile was observed till 18$^{th}$ day in in-vitro studies (Guler et al., 2025).

Cationic nanoliposomes prepared using DPPC, DOTAP, and cholesterol was loaded with artesunate showed promising effect as anti-pyroptosis and anti-inflammatory agent by inhibiting NLRP3 inflammasome activation (Attia et al., 2025). Nanomicelles loaded with arimoclomol was shown to have promising anti-inflammatory effect in AD and PD conditions (Xavier-De-Britto et al., 2025). Nanostructured lipid carriers loaded with xanthohumol enhanced the drug's oral bioavailability and therapeutic activity by ameliorating oxidative stress, neuroinflammation, amyloid aggregation, and AChE inhibition in aluminum chloride-induced AD rats (Khandale et al., 2025). Dendrimers are hyperbranched polymer forming a globular structure in nanometer range. They have a core structure to which multiple branches of polymer are attached. To the terminal branch groups, ligand attachment is observed by ionic interactions or covalent bonding and the encapsulation can also happen in the internal void spaces between the branches by non-covalent interactions. The system may respond to alteration in pH, enzymatic degradation or redox potential. Poly(propylene imine) (PPI), polyamidoamine (PAMAM), and poly-L-lysine (PLL) are the most widely accepted systems for dendrimer preparation and functional group modification (Arbez-Gindre et al., 2023).

PAMAM-calix-dendrimer was developed as a universal drug with choline esterase inhibition action with $IC_{50}$ value in the range 0.076-5400 μM (Shiabiev et al., 2025). Tacrine and other choline esterase inhibitors have been limited due to their hepatotoxicity. Therefore, PPI G5.0 dendrimers conjugated with oleic acid were used as a brain targeting system with tacrine loaded into the system by physical encapsulation for intranasal administration (Sahu et al., 2024). A nanocomplex built by complexing carbon quantum dots with PAMAM dendrimers via electrostatic interaction has shown to be a promising theranostic nanocarrier for disease treatment (Sonam et al., 2024). Inorganic nanoparticles like gold NPs, silver NPs, magnetic NPs, quantum dots, graphene oxide, black phosphorus nanosheet, mesoporous silica NPs, etc., have evolved to be effective therapeutic agents for neurodegenerative disease management. Magnetic NPs, made from ferrites, metals, alloys, or metal oxides, efficiently deliver genetic components to the brain. Semiconductor NPs, i.e., quantum dots, have photoluminescence characteristics which have been explored for deep tissue imaging for diagnostic purposes (Naimi et al., 2024).

Thus, we can say that nanoparticles are a promising drug delivery system for the agents that are designed for the treatment of neurodegenerative conditions like AD. These offer a range of benefits like improved BBB permeability, enhanced pharmacokinetic properties of the drug, sustained release offers better patient compliance, therapeutic targeting, and personalized treatment improves the AD therapeutic efficacy. The unprecedented adverse effects occurring due to smaller particle size and accumulation in untargeted organs should not be overlooked, besides defining the exact mechanism of action. Hence, thorough preclinical and clinical studies should be carried out to avoid any fatal untoward effects.

## 6. Nucleic acids and their delivery to the brain in AD

The ability of nucleic acids to treat the disease at the genetic level helps in developing a more precise and personalized treatment for chronic conditions like AD. It offers several advantages like precise targeting of genes due to base-pairing function, easier protein binding due to ease in conformation adaptation like the target protein, higher success rate as a therapeutic agent due to its specificity, and longer half-life. RNA-targeted nucleic acid drugs include antisense oligonucleotides (ASO), small interfering RNA (siRNA), and microRNA (miRNA), which act by inhibiting target RNA binding to target genes. Clustered regularly interspaced short palindromic repeats (CRISPR) cas systems seem to be the most promising approach for neurodegenerative disease and cancer management. They can target the upregulated or the downregulated genes expressed in disease conditions and help in regulating these gene expressions. Plasmid DNAs (pDNA) and messenger RNA (mRNA) are used to increase the expression of target genes. Besides these agents, peptides like TLQP-21 (VGF precursor), verubecestat (BACE1 inhibitor), semagacestat (γ-secretase inhibitor), aducanumab (Aβ-targeted monoclonal antibody), glucose-dependent insulinotropic polypeptide (GIP, peptide hormone), GIP analogues (D-ALA2-GIP, dAla2-N-AcGIP), dual GIP/GLP-1 receptor agonists (DA3-CH, DA4-JC), anti-amyloid therapy (gantenerumab, GV-971), troriluzole (glutamate modulator), suvorexant (orexin antagonist), and AADvac1 (active anti-tau vaccine) have also been preclinically and clinically tested for AD therapy (Mota et al., 2023).

### a. siRNA and miRNA

RNA interference, used by siRNA and miRNA, is a cellular mechanism to repress gene expression by inhibiting mRNA expression or promoting target mRNA degradation. In the cytoplasm, Dicer (ribonuclease III enzyme) mediated cleavage of dsRNA leads to generation of dsRNA of 18-25 nt length and with 2 nucleotide 3' overhang. These dsRNA's then bind to RNA-induced silencing complex (RISC). In case of siRNA, the sense strand is degraded by argonaute 2 (AGO2) while in case of miRNA, the sense strand is released. Later, the antisense strand of siRNA guides towards the target mRNA and the siRNA-RISC-AGO2 complex cleaves the target mRNA and leads to gene silencing. In contrast the miRISC complex recognizes the target mRNA and silences the target by translational repression and degradation principally, but in rare cases AGO2-mediated degradation may also be observed for miRNA (Lam et al., 2015). Nuclease-mediated degradation of siRNA is a major clinical challenge that can be tackled by chemically modifying the siRNA strand (Petri and Meister, 2013). The miRNA has a higher tendency to activate immune response, causing

adverse effects. This can also be managed using a chemical modification technique. The role of miRNA and siRNA as diagnostic tools is vast and beyond the scope of this review work. Hence, we will provide details about the delivery systems developed for miRNA and siRNA therapy.

A biochip consisting of miRNA-135a-5p was developed for early-stage AD detection using faraday effect (magneto-optical) and magnetoplasmonic nanoparticles (Lin et al., 2025). Similarly, a hydrogel-based sensor was developed that can detect miR-574-5p in the blood as early-stage AD biomarker (Lim et al., 2022). Lentiviral-mediated miR-31 delivery in 3xTg-AD mice's hippocampus (stereotactic surgery) mitigated the APP and BACE1 pathology, besides improving neurobehavioral performances (Barros-Viegas et al., 2020). A group of scientists loaded curcumin and miRNA-124 for co-delivery using red blood cell membrane (RBCm)-coated HMPB (hollow mesoporous Prussian blue) nanoparticle, which could mimic Aβ transportation, bypassing the BBB and accumulating in neurons and microglia by advanced glycation end products (RAGE) receptor binding. This ameliorated the Aβ pathology and shifted the proinflammatory M1 microglial polarization towards anti-inflammatory M2 microglia (Song et al., 2025). miR-129-5p is an important regulator of immune responses in the brain, which, when combined with biodegradable poly(lactic-co-glycolic acid) to develop a nanoparticle system, resulted in synergistic anti-inflammatory action by regulating the immune response and promoting microglial polarization into a pro-regenerative phenotype (Kalashnikova et al., 2023). Liposome-mediated delivery of miR-195 using polyethyleneimine/miR-195 encapsulation technique with cell-penetrating peptide (p-aminophenyl-alpha-d-mannopyranoside and cationic cell penetrating peptide) modification resulted in cognitive decline alleviation comparable to aducanumab in APP/PS1 mice (Su et al., 2024).

Intracerebroventricular delivery of miR-23b-3p in APP/PS1 mice was able to ameliorate tau pathology, cognitive dysfunction, and histological alterations through GSK-3β mediated tau phosphorylation action (Jiang et al., 2022). miR-17 inhibitor (antagomir) was delivered through microglia targeting using mannose lipid nanoparticles by injecting it into intracisternal magna in 5XFAD AD mice model. It dampened the microglia-mediated inflammatory action and thereby diminished the Aβ pathology. It also enhanced synaptic function, ameliorating the anxiety and spatial memory behavioral performances (Badr et al., 2024). Morpholino-miR-186 nanoconjugate developed on conjugation with biodegradable, amphiphilic, and multivalent poly(β-L-malic acid-trileucine)-copolymer. The miRNA was delivered to the brain through LRP-1 transcytosis pathway (Israel et al., 2023).

Delivery targeting RNA interference through siRNA has also seen significant development in recent years. Rabies virus glycoprotein (RVG29)-decorated liposome was developed as a non-viral virus-mimic gene vector to deliver BACE1 siRNA to the brain. The bioinspired liposome system consisted of cholesterol, DSPE-PEG (2000)-DBCO, and DOTAP polymers. The delivery system successfully delivered the siRNA to the brain observed through marked suppression of BACE1 both at mRNA and protein levels (Erel-Akbaba et al., 2025). Halloysite (nanoclays) nanotube tends to absorb Aβ and inhibit fibril generation and aggregate clearance. Similarly, RVG29 (brain penetrating peptide derived from rabies virus glycoprotein) can also bind to Aβ directly. Exploiting this property of halloysite and RVG29, a system was built by functionalizing RVG29 onto short halloysite nanotubes for the delivery of Ripk1 siRNA. The siRNA was loaded into the lumen of the nanotube to prevent its degradation. This system was able to ameliorate the Aβ plaques and protect the neurons from necrotic cell death (Wu et al., 2024). Besides RVG, RDP is another polypeptide derived from rabies virus glycoprotein, which tends to bind to nicotinic acetylcholine receptor (nAChR). RDP and its derivative RDP-oligoarginine peptide are being explored for their brain targeting efficiency and their potential to be used as siRNA delivery vehicle for glioma cells and brain targeting. siRNA binds to the polypeptide through electrostatic interactions forming a nanoparticle system (L. Chen et al., 2025).

Poly(2-(N, N-dimethylamino) ethyl methacrylate was conjugated with CGN and QSH peptide (for brain penetration and Aβ binding, respectively) and siRNA. This system helped to prevent the enzymatic degradation of siRNA and aided in the cellular uptake of siRNA. BACE1 knockdown was seen upon

intravenous administration of this formulation to transgenic AD mice (Zheng et al., 2017). BACE1 targeted siRNA was loaded in a nanocarrier designed on PEGylated (poly(2-(N, N-dimethylamino) ethyl methacrylate) polymer with CGN brain penetrant peptide and Tet1 neuron-specific peptide. They were internalized into the cell by endocytosis (clathrin-mediated) and micropinocytosis. When administered in APP/PS1 transgenic mice, this nanocomplex ameliorated BACE1 mRNA levels and also reduced the amyloid plaque levels (Wang et al., 2018). Carboxymethylcellulose encapsulated siRNA, fingolimod, and zinc oxide nanoparticles into a polymeric matrix were able to alleviate microglia priming, promote Aβ phagocytosis, and increase BDNF secretion, proving the efficiency of this CMC-hybrid nanoparticle delivery system in AD (Aljohani et al., 2024). Polyethyleneimine (PEI) polymer was hydrophobically modified using stearic acid or dodecylacrylamide to develop a nanocarrier (polyplexes) system for siRNA delivery across BBB (Hartl et al., 2023). Exosomes are also emerging as an exciting vehicle for drug delivery. Colostrum-derived exosome-based nanoparticle system was built on PEI polymer matrix which could be used for plasmid DNA and siRNA deliveries, and it also simulated the viral gene expression and facilitated the siRNA therapeutic screening. In a study, SARS-CoV-2 spike protein and nucleocapsid protein encapsulated in the exosome nanoparticle system led to antibody generation in an in-vivo experiment against the viral antigen, suggesting the efficiency of the delivery system for viral protein delivery with a reduced virulence efficiency and risk (Wallen et al., 2022). Polypyrimidine tract-binding protein-1 (PTBP1) is an important regulator of neurogenesis and tumor progression events by regulating alternative splicing cycles. Its downregulation converts astrocytes to functional neurons, although the mechanism remains unclear. Therefore, studies were reported where siRNA against PTPB1 was delivered to invitro and in-vivo models through a cationic biomimetic triblock polypeptide system of polyethylene glycol, polylysine, and polyleucine ($PEG_{44}$-$PLL_{30}$-$PLLeu_{10}$) with astrocyte membrane coated to deliver siRNA against PTPB1, regulating the glutamate transport mechanism in biological systems (Y. Liu et al., 2025). Similarly, rho-associated kinase (ROCK) I and II inhibition has been reported to suppress axon regeneration and Aβ formation, respectively. A PEG-PEI/ROCK-II-siRNA complex was synthesized, which was able to successfully deliver the ROCK-II siRNA to the cytoplasm and synapse of the cells (Liu et al., 2013). The uses of nucleic acid and peptide as therapeutic agents are represented in Figure 1.

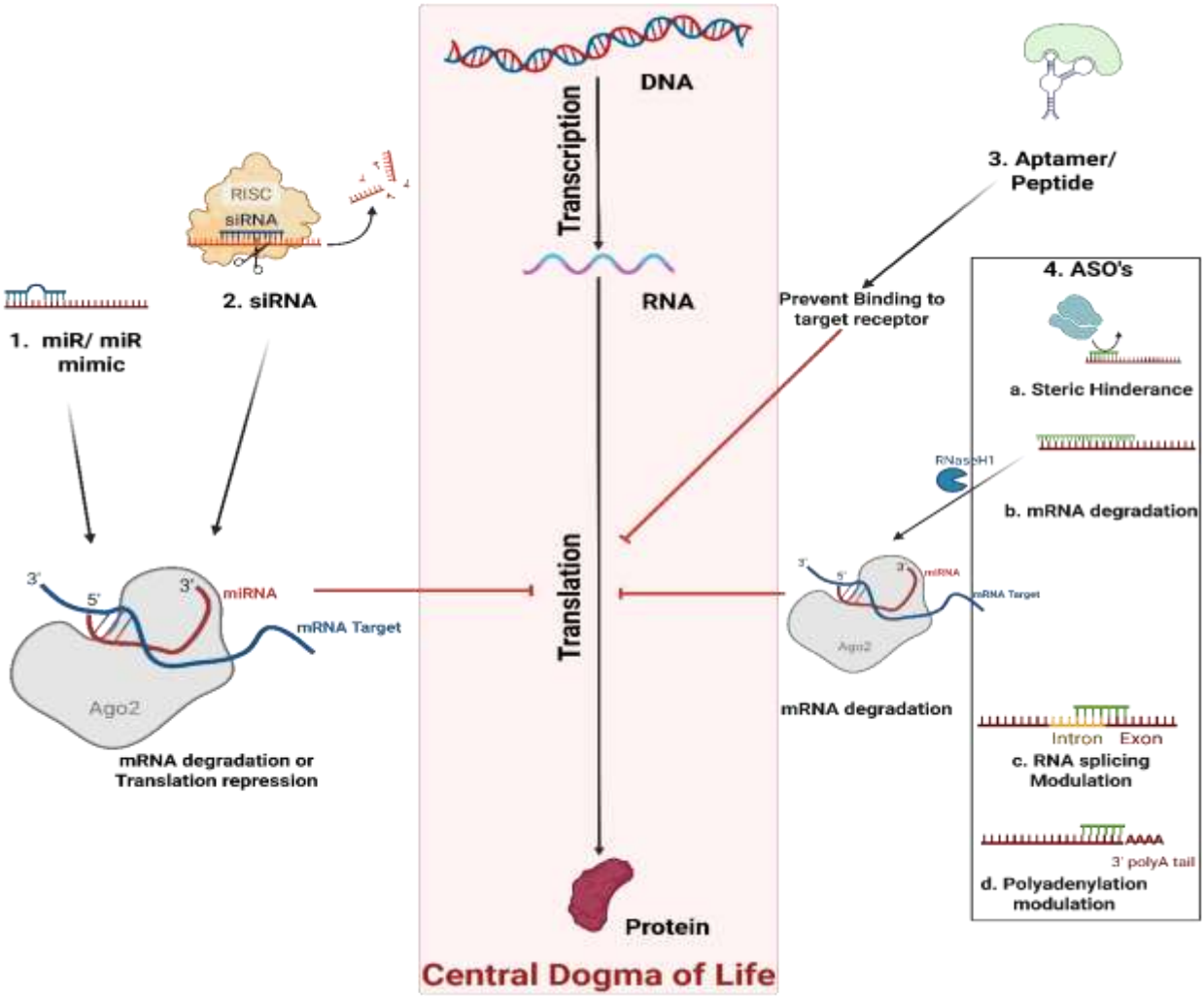


**Figure 1: Mechanism of Action Nucleic Acid in AD Management:** The cell's central dogma revolves around DNA-to-RNA transcription and RNA-to-protein translation. Peptides and nucleic acids act directly by inhibiting the translation process. The agents used include miRNA and siRNA (which directly inhibit the mRNA translation by causing its degradation with the help of the RISC complex). ASOs also act by steric hindrance, RNA splicing alteration, and polyadenylation modification mediated mRNA degradation. Besides these nucleic acids, protein derivatives like aptamers also inhibit protein translation by acting directly at the receptor interaction. The translational inhibition leads to repressed protein expression and hence, ameliorated pathological responses.

### b. Antisense oligonucleotide

Antisense oligonucleotides (ASOs) are synthetic forms of DNA or RNA designed to modulate gene expression by targeting mRNA, ribosomal RNA (rRNA), miRNA, Piwi-interacting RNAs (piRNA), and small nuclear RNAs (snRNAs). Nuclease-mediated degradation of the ASOs' phosphodiester bond makes it inefficient as a therapeutic agent, where PS linkages instead of diester bonds prove to be beneficial. Principally, ASOs act by different mechanisms targeting mRNA and miRNA. RNase H1 enzyme-mediated cleavage of RNA/DNA duplexes like target mRNA using complementary pairing. While for the miRNA-like molecules, ASOs first form a double-stranded RNA-DNA complex, which is further cleaved by the RNase H1 enzyme. ASO can also act without causing degradation, by simply occupying the 5' cap or polyadenylated tail of mRNA's hindering the translation process (Bennett and Swayze, 2010; Crooke et al.,

2021). Spinraza (Nusinersen) is an example of occupancy-mediated action, FDA-approved drug used for spinal muscular atrophy (Darras et al., 2019). The mRNA therapy uses single-stranded polynucleotide (~500-5000nt), which can be translated in the target cell's cytoplasm without affecting the genetic makeup, as no nuclear participation is required. The major hurdle encountered with mRNA delivery is its susceptibility to undergo enzymatic degradation due to its anionic nature. Lipid nanoparticle-mediated delivery system has been successfully implemented for delivering the mRNA vaccine for COVID-19 (BNT162b). Similarly, lipids, lipid-like materials, biomaterials, polymers, and proteins can be utilized to develop mRNA therapy delivery systems (Lu et al., 2023). $ApoB^{[11]}$ peptide is an effective vector for transporting antibodies, tropic factors, proteases, and other peptides through the BBB through LDL-receptor binding.

This peptide was modified by the addition of 9 arginine residues to the C-terminal as a positively charged tail and 5 glycine linkers as a flexible anchor. 2'-OMe modified antisense oligonucleotide against 168-186 nucleotides of α-synuclein (α-Syn) was chosen for delivery using the ApoB-peptide delivery system. This system was able to successfully downregulate the α-Syn expression and prevent plaque accumulation through glial response suppression. (Leitão et al., 2023). L-type amino acid transporter 1 (LAT1) is an important tool for brain targeting for ligands and polyionic complexes. LAT1 targeting ASO was encapsulated inside nanoparticles in combination with phenylalanine, which was used as a LAT1 binding enhancer (Lim et al., 2024). Another study reported use of cationic liposomes for TREM2-lowering ASO and resveratrol co-delivery for immune suppression action, acting as a nanomodulator. This complex crossed the BBB through endothelial cell binding via D-T7 peptide. This system was successful to deliver the therapeutic agents to the M1 phenotype of microglia ameliorating the cognitive dysfunction in APP/PS1 mice (Wei et al., 2025). Multichannel polyion complex was developed using cationic co-polymer poly(ethylene glycol)-b-poly[N-(N'-{N"-[N"'-(2-aminoethyl)-2-aminoethyl]-2-aminoethyl}-2-aminoethyl) aspartamide]- cholesterol, RVG20, and Tet1 peptide for dual targeting brain delivery using nAChR and GT1B receptors (Jia et al., 2024).

### c. Nucleic Acid Aptamers

Aptamers are single-stranded DNA/RNA molecules synthetically derived against a specific target protein and have a high binding affinity and specificity. Amyloid pathology-targeted aptamers are being designed for early diagnosis and treatment of AD. $A\beta_{40}$ and $A\beta_{42}$ are both pathological forms of amyloid protein, where $A\beta_{40}$ is the abundantly produced form, while $A\beta_{42}$ has faster aggregation kinetics, making it more toxic. Several RNA (B55, N2, E2, KM33, KM41, E22P-AbD43) and DNA (T-SO508, RNV95, Aβ-79-1H1) are designed to target these protein aggregates and inhibit their further accumulation and guide them towards cellular metabolism and autophagy (Zheng et al., 2022). Several studies have been published where a combination of the previously mentioned methods has been used for brain delivery and AD management. A nanocomplex was assembled by electrostatic force between octaarginine's hydrophobic derivative conjugated chemically to lauric acid and the target RNA. The stability was further enhanced by polyethylene glycol-polyglutamic acid or hyaluronic acid for muco-diffusion through the nasal mucosa of the olfactory tract.

This system protected the RNA from degradation, preserving its physicochemical characteristics, and prevented premature release of RNA in the ex vivo system. The miRNA mimic was successfully delivered to the mouse hippocampus and ameliorated the AD pathology (Samaridou et al., 2020). Extracellular vesicles (EVs) also prove to be a promising vehicle for the delivery of peptides and nucleic acids to the brain. Small EV consisting of brain-derived neurotrophic factors (BDNF), secreted from mesenchymal stem cells, provided neuroprotection and anti-inflammation activity in ischemic stroke mouse model when administered intranasally (Zhou et al., 2023). A cell-penetrating peptide (RVG9R) was complexed with BACE1 siRNA, which was further encapsulated using chitosan-coated and uncoated solid lipid nanoparticles. The formulation, when administered for nose-to-brain delivery, was able to exploit the trigeminal nerve pathway and olfactory nerve pathway (Rassu et al., 2017). Fingolimod conjugated

biguanide ROS-responsive system was used as a nanoparticle carrier for siRNA against BACE1 where N-acetylcysteine was used as mucolytic agent. Electro-positivity of nanocarrier and mucolytic activity together enhanced brain permeation of the whole system. The nanocarrier responded to ROS at pathological site and released siRNA at the target along with fingolimod, ameliorating the cognitive dysfunction in AD mice (Y. Chen et al., 2025). Another nose-to-brain delivery platform was built based on lipid nanoparticles using microfluidic method co-encapsulating α-mangostin and BACE1 siRNA.

The receptor-mediated transcytosis mechanism was used by the system for brain targeting. It promoted microglia-mediated phagocytosis and autophagy-mediated Aβ degradation, while the BACE1 expression was suppressed and hence, synthesis of senile plaque was also diminished in APP/PS1 mice (Xu et al., 2025). DP7-C (cell penetrating peptide), when enveloped with hyaluronic acid, led to the formation of a nanomicelle with a multifunctional core-shell structure. The system can bind to CD44 for cellular uptake and was successful in delivering siRNA to the brain through the trigeminal nerve (Yang et al., 2022). Assembled nanoparticles were developed using stearic acid-modified functional peptide and methoxy-polyethylene glycol-polycaprolactone polymer. To these assembled nanoparticles, ASO was loaded using electrostatic interaction, which showed good nose-to-brain targeting (Iioka et al., 2025). Liposomes made with a unique phospholipid mixture have been designed to mimic the naturally occurring exosomes. These exosome-like liposomes have been used for curcumin encapsulation, which targeted the amyloid pathology, providing anti-inflammatory and antioxidant action in the in vitro studies (Fernandes et al., 2021).

## Conclusion and Prospects

Neurodegenerative conditions like AD and PD have no cure due to their multifaceted nature. The treatments are ineffective currently as they merely target the symptomatic relief but could not retard the pathological progression. Agents like Memantine (AChE inhibitor) had great therapeutic potential, but their clinical application was limited due to their adverse effects. In such conditions where no curative drugs are available for management, then increasing the efficacy, through pharmacokinetic and pharmacodynamic modulation, of the available agents is the only savior for clinical cases. Advancing nanotechnology has helped as an efficient management option for AD. Consequently, designing therapeutic peptides and nucleic acid-targeted therapy has served as a boon in AD therapeutic evaluation. in the past two decades, several macromolecules have been proven effective for AD management. The FDA approval of aducanumab has proved to be ground-breaking research in AD therapy. The review has provided a newer avenue for AD therapy, which suggests the application of nucleic acids, peptides, and combining them with a nanotechnology approach could make the AD treatment more promising. Despite such promising results, one should always take into consideration the therapeutic window for the dosage form, unforeseen side effects, synergistic or complementary action between the therapeutic agent and the dosage form, and a regulated system for formulation. We can say that limited resources are available for the regulation of nanoparticles and nucleic acid or peptide in therapy; further studies in this direction will be clinically beneficial in the long run. Formulation stability, cellular permeability, patient compliance, and mucociliary clearance (in case of nasal formulations) are to be considered thoroughly for CNS applications.

## Conflict of Interest

The authors declare no existing competing interest.

## Author contributions

The paper's initial draft was written by the first author under the guidance of a cross-responding author. Each author wrote a portion of the manuscript, collected data, edited it, created tables, and was given permission to submit it to a journal for publication.

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## Ethical Approval

Not Applicable

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