Current opinion in Alzheimer's disease therapy by nanotechnology-based approaches

Shakeel Ahmed Ansari[a], *Rukhsana Satar*[b], *Asma Perveen*[c], *and Ghulam Md Ashraf*[d]

Purpose of review
Nanotechnology typically deals with the measuring and modeling of matter at nanometer scale by incorporating the fields of engineering and technology. The most prominent feature of these engineered materials involves their manipulation/modification for imparting new functional properties. The current review covers the most recent findings of Alzheimer's disease (AD) therapeutics based on nanoscience and technology.

Recent findings
Current studies involve the application of nanotechnology in developing novel diagnostic and therapeutic tools for neurological disorders. Nanotechnology-based approaches can be exploited for limiting/reversing these diseases for promoting functional regeneration of damaged neurons. These strategies offer neuroprotection by facilitating the delivery of drugs and small molecules more effectively across the blood–brain barrier.

Summary
Nanotechnology based approaches show promise in improving AD therapeutics. Further replication work on synthesis and surface modification of nanoparticles, longer-term clinical trials, and attempts to increase their impact in treating AD are required.

Keywords
Alzheimer's disease blood–brain barrier, drug delivery, nanotechnology

INTRODUCTION

Alzheimer's disease (AD) is a common neurological condition affecting approximately 35 million people worldwide at present, and is expected to affect 60 million individuals by 2050 [1]. AD is characterized by a gradual onset of neurocognitive symptoms, which are slowly progressive and ultimately result in total incapacitation of the individuals' functioning [2,3]. The pathologic changes in AD are spread throughout the brain, resulting in a generalized loss of cortical grey matter and an early loss of basal forebrain cholinergic neurons [4]. At neuropathological level, AD is primarily characterized by accumulation of misfolded proteins such as amyloid β (Aβ) in plaques and tau in neurofibrillary tangles. According to one proposed mechanism, Aβ deposition is the first pathogenetic event occurring years before the appearance of clinical symptoms, and tangles are the driving force in progression toward detectable clinical symptoms [5,6▪▪]. Aβ length may varies from 38 to 43 amino acid residues, which is generated from amyloid precursor protein (APP) via sequential proteolytic cleavage [7]. The significance of Aβ and tau in AD development and progression can be understood by the fact that their concentrations in cerebrospinal fluid (CSF) starts changing some 15–25 years before the onset of clinical symptoms [4].

The ever-growing prevalence and harmful impact of AD on global population has been a great matter of concern for researchers. However, most of the therapeutic strategies proposed by researchers

[a]Center of Excellence in Genomic Medicine Research, King Abdulaziz University, [b]Department of Biochemistry, Ibn Sina National College for Medical Studies, Jeddah, Saudi Arabia, [c]Department of Biochemistry, Faculty of Life Sciences, Aligarh Muslim University, Aligarh, Uttar Pradesh, India and [d]King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia

Correspondence to Ghulam Md Ashraf, PhD, Assistant Professor, King Fahd Medical Research Center, King Abdulaziz University, P. O. Box 80216, Jeddah 21589, Saudi Arabia. Tel: +966593594931; e-mail: gashraf@kau.edu.sa, ashraf.gm@gmail.com

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KEY POINTS

- There is considerable focus on designing and surface modification of nanoparticles systematically to bind and transport greater amount of drugs across the BBB for treating Alzheimer's disease.
- Nanotechnology offers the promise of targeting the early stages of Alzheimer's disease by noninvasive-diagnostic methods.
- Further research on magnetic and nonlinear optical properties of nanoparticles is necessary to extend their utility in bioimaging, labeling, and preparing novel drug delivery systems for treating neurodegenerative disorders.

have failed to modify the course of AD. Nanotechnological approach for AD therapy is one such quest that has gained attention of late with some encouraging success. In the present review, we have explored recent developments in nanotechnology based AD therapy.

NANOTECHNOLOGY-BASED DRUG DELIVERY SYSTEMS FOR ALZHEIMER'S DISEASE THERAPY

The use of innovative nanoparticle (NP)-based drug delivery systems to promote drug penetrance across the blood brain barrier (BBB) could be considered as a strategic approach in the diagnoses, prevention, and treatment of AD. Therefore, biodegradable and biocompatible nanocarriers such as liposomes, polymeric NPs, solid lipid NPs or micelles were proposed to protect and transport drugs to cure AD (Table 1). The developed nanosystems have shown significant improvement in the physicochemical characteristics of drugs such as its hydrophilicity or lipophilicity, ionization, high molecular weight, poor bioavailability, extensive metabolization and other adverse effects, in order to give a positive pharmacotherapeutic impact on patients with AD [7,8,9]. Figure 1 summarizes the major nanotechnology based AD therapies.

Polymeric NPs

Polymeric NPs are concerned with preparation of particulate dispersions ranging from 1 to 1000 nm. They are obtained by techniques like ionic gelation, emulsion solvent evaporation, polymer polymerization, spray drying, and nano precipitation [41,42]. One of these approaches i.e. emulsion polymerization technology was used to synthesize poly(*n*-butyl cyanoacrylate) NPs which were surface modified by polysorbate 80. The resulting NPs were exploited to obtain higher loads of tacrine and rivastigmine for treating AD. This is made possible by acquiring the efficient interaction between the endothelial cells of the brain micro vessels and polysorbate 80 coating [31,33]. Similarly, Zhang *et al.* modified the surface of poly(lactic acid) polymeric NP by polyethylene glycol (PEG) and conjugated a 12-amino acid peptide, TGNYKALHPHNG (denoted as TGN) and QSH (targeting peptides) on these NPs. It was observed that QSH exhibited high affinity for $A\beta_{1-42}$, which is a component of amyloid plaques. The TGN specifically targets the ligands at the BBB. *In vivo* results suggested encouraging reports in which NPs treated amyloid plaques with greater sensitivity and improved mode of drug delivery [29▪]. These findings were extended by using intranasal NPs for delivering basic fibroblast growth factor (bFGF), which facilitates selective binding of *N*-acetylglucosamine to nasal epithelial membrane for brain delivery. The intranasal administration of *Solanum tuberosum* lectin modified NPs resulted in five-fold greater distribution in the brain as compared to their intravenous administration [27]. In another approach, poly[(hexadecyl cyanoacrylate)-*co*-methoxypoly(ethylene glycol) cyanoacrylate] NPs were designed for slowing down and disrupt the aggregation process of $A\beta_{1-42}$ peptide [35]. In addition, these studies were incorporated by work undertaken for bioavailability of rivastigmine via intranasal route to the brain [34]. More recently, a highly specific binding of curcumin was obtained by superparamagnetic iron oxide NPs coated with polyethylene glycol-polylactic acid and polyvinylpyrrolidone for detecting amyloid plaques [43]. It was observed that the resulting formulation exhibited no cytotoxicity in human neuroblastoma cells (SH-SY5Y) and disappearance of amyloid plaques in nontransgenic mice.

Solid lipid nanoparticles (SLNPs)

SLNPs are obtained from emulsifying agents, lipids, and water/solvent by various methods including evaporation method, solvent emulsification–diffusion method, spray-drying method, double emulsion method, high pressure homogenization, and ultrasonication/high-shear technique [44].

Owing to the excellent penetration ability of SLNPs to bypass the BBB, piperine SLNPs were synthesized by emulsification-solvent diffusion method and coated with polysorbate 80 [38]. Sood *et al.* developed curcumin/donepezil-loaded SLNPs for delivering the drug in higher concentration inside the brain via intranasal route. Results showed that memory and learning were improved with this

Table 1. Nanotechnology-based systems used for AD therapy

Nanotechnology based approaches	Agents	Administration route	Applications	References
Liposomes	β-sheet blocker peptide	In vitro	Crossed a BBB model	[8]
	Curcumin	In vitro	Prevented amyloid aggregation	[9]
	Curcumin–PEG derivative	In vivo	Ability to promote Aβ aggregation	[10]
		Ex vitro	Higher affinity by senile plaques	
			Intaken by the BBB model	
	Curcumin-phospholipid conjugate	Hippocampal injection	Stained the Aβ deposits in brain of mice	[11]
		Ex vivo	Strongly labeled Aβ deposits	
	Folic acid	Intranasal	Absorbed through the nasal cavity	[12]
	Galantamine and a ligand-functionalized peptide	In vitro	Uptake into PC12 neuronal cells	[13]
	Ginkgo biloba extract	Oral	Accumulated in the brain	[14]
			Increased the activities of antioxidant enzymes	
			High concentration of flavonoid glycoside biomarker in the brain	[15]
	Lipid–curcumin derivatives	In vitro	Higher affinity for Aβ1–42 fibrils	[16]
	Rivastigmine	Intranasal	Enhanced drug pharmacodynamics in mice	[17]
		Intranasal	Higher concentrations in olfactory region, hippocampus and cortex	
		Oral	Improved memory and cognitive functions	[18]
		Intranasal	Highest AChE inhibition	[19]
		Intravenous	Enhanced bioavailability	
		Oral and intraperitoneal	Highest AChE inhibition	[20]
		In vitro	Drug permeated through cultured Caco-2 cells	
		Oral	AChE inhibited in the brain	[21]
	Transferrin MAb and PAA	In vitro	Crossed a BBB model by transcytosis pathway	[22]
		Intravenous	Enhanced brain targeting	
Liquid crystals	*T. divaricate*	Transdermal	Increased skin permeation and retention	[23]
			Stability of drug in formulations	
Microemulsions	Tacrine	Intranasal	Improved memory	[24]
			Rapidly absorbed through nose to brain	
Nanoemulsions	β-Asarone	Intranasal	Improved bioavailability	[25]
	Curcumin		Improved memory and learning	
	Huperzine A	Transdermal	Improved cognitive function	[26]
	Tabernaemontana divaricate		Increased skin permeation and retention	[23]
			Stable formulations	
Polymeric NPs	Fibroblast growth factor	Intranasal and intravenous	Increased ChAT	[27]
			Increased biodistribution with intranasal administration	

Table 1 (*Continued*)

Nanotechnology based approaches	Agents	Administration route	Applications	References
	Idebenone	In vitro	Decreased drug reactivity	[28]
			Increased drug stability	
	Peptides TGN and QSH	Intravenous	Targeted delivery to amyloid plaques	[29▪]
	Rivastigmine	Intravenous	Improved learning and memory capacities	[30]
			High concentrations of rivastigmine achieved in the brain	[31]
		Intranasal	Enhanced uptake into the brain	[32]
			Improved bioavailability	
	Tacrine	Intravenous	High concentrations of tacrine achieved in the brain	[33]
			Reduced the total dose required for the therapy	
	Unloaded polymeric NPs	In vitro	Disaggregation of Aβ (Aβ1–42)	[34,35]
Solid lipid NPs	Curcumin	Oral	Increased AChE activity	[36]
			Increased biodistribution in the brain	
	Curcumin and donepezil	Intranasal	Higher levels of acetylcholine in brain	[25]
			Improved memory and learning in mice	
			Increased concentration of drugs in the brain	
			Reduced oxidative damage	
	Ferulic acid	In vitro	Higher protective activity on neurons	[37]
	Huperzine A	In vitro	Permeation through abdominal rat skin	[26]
		Skin application	No primary irritation observed	
			Improved cognitive functions	
	Piperine	Intraperitoneal	Increased AChE enzyme activity	[38]
			Reduced plaques and tangles in the brain	
	Resveratrol	Oral and intraperitoneal	Improved cerebral bioavailability	[39]
			Improved memory	
	Vinpocetine	Oral	Enhanced bioavailability compared to the free drug	[40]

novel nanoformulation [25]. Frozza *et al.* developed SLNPs with oil-based cores loaded with resveratrol [39]. The idea was to see if cerebral bioavailability could be increased with this formulation. Indeed, the results showed between 3-6 times greater drug concentrations in organs like kidneys, liver, and brain. These SLNPs had shown improvement in memory deficits as a result of an intracerebral infusion of $A\beta_{1-42}$ in the mouse models. These studies demonstrate the potential of resveratrol loaded nanocarriers in AD. As a variation of such studies, Patel *et al.* investigated the effect of huperzine A-loaded lipid-based nanocarriers through *in vitro* and *in vivo* approaches [26]. *Ex vivo* permeation studies showed that the formulated nanocarriers showed enhanced permeability in the abdominal skin of rats. An improvement in cognitive function was seen in addition as a result of sustained and controlled release of drug from the developed nanocarriers via the transdermal route [45].

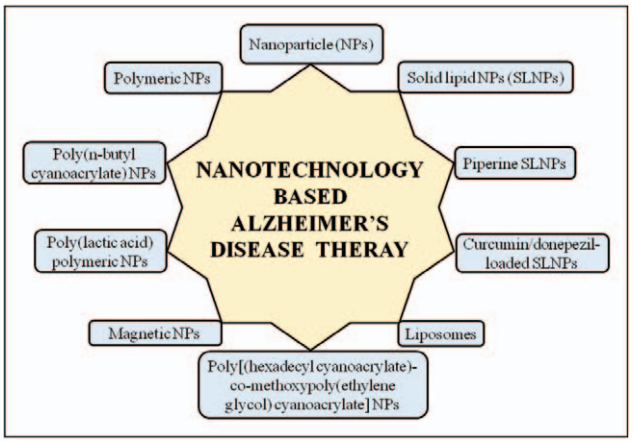

FIGURE 1. Nanotechnology based Alzheimer's disease therapies.

Studies have demonstrated that curcumin decreases the *in vitro* and *in vivo* Aβ formation from amyloid precursor protein, and also inhibits the aggregation of Aβ into pleated sheets [46,47]. Hence, Kakkar *et al.* incorporated curcumin into SLNs for brain delivery in rats via the oral route [36]. They observed that curcumin-loaded SLNs increased the activity of acetylcholinesterase in comparison with free drug. The concentration of curcumin was increased by two-fold in the brain.

Liposomes

Liposomes are vesicles consisting of one or more phospholipid bilayers which are concentrically oriented around an aqueous compartment to serve as carriers of lipophilic or hydrophilic drugs [48]. Researchers have prepared rivastigmine liposomes and cell-penetrating peptide-modified liposomes for improving the distribution of rivastigmine in the brain in order to enhance its pharmacodynamics via intranasal administration and minimize its side effects [17]. It was observed that the modified liposomes improved brain delivery as well as enhanced pharmacodynamics across BBB when used through nasal olfactory pathway into the brain. Alternately, liposomes were functionalized with the help of cell-penetrating TAT peptide with great success [9]. Monoclonal antibodies (mAb) were also explored in liposomes loaded with curcumin analog and comparison was made for curcumin analog and curcumin-loaded liposomes. mAb modified liposomes showed better affinity for senile plaques. However, observations were made on postmortem brain tissue of patients with AD. An improved intake of curcumin across the BBB cellular model was significantly evident [10]. Similarly, galantamine was tagged to functionalized nanoliposomes by Mufamadi *et al.* in order to facilitate its uptake into PC12 neuronal cells for demonstrating the effectiveness of the nanosystems [13].

More recently, IRL-1620 peptide had shown promise in reversing neuronal death by increasing the blood flow to the brain via dilating or widening of blood vessels. However, its half-life is 7 min and it could not penetrate the BBB. Hence, this peptide was packaged into liposomal nanocarriers to overcome these drawbacks, and their viability was checked against PC-12 neuronal cell line [49]. It was observed that liposomal IRL-1620 was more effective in maintaining PC-12 cell viability as compared to the free drug due to enhanced drug delivery. Nanocarriers allowed the differentiation of PC-12 cells to utilize the drug more effectively. H102, a novel β-sheet breaker peptide, was encapsulated into liposomes to reduce its degradation and increase its brain penetration by intranasal administration for AD treatment. Their transport characteristics were evaluated on Calu-3 cell monolayers. The neuroprotective effects were tested by detecting acetylcholinesterase (AChE), choline acetyltransferase (ChAT), and insulin degrading enzyme (IDE) activity. It was observed that the prepared liposomes could penetrate Calu-3 cell monolayers consistently. After intranasal administration, H102 could be effectively delivered to the brain, and the AUC of H102 liposomes in the hippocampus was three-fold higher than the solution group. H102 liposomes could excellently ameliorate spatial memory impairment of AD model rats, increase the activities of ChAT and IDE, and inhibit plaque deposition, even in a lower dosage compared with H102 intranasal solution [50]. These findings suggest that multifunctional liposomes seem to have encouraging prospects in AD research.

RECENT NANOTECHNOLOGY BASED THERAPEUTIC APPROACHES FOR ALZHEIMER'S DISEASE THERAPY

The demonstration of the pathophysiologic association of oxidative stress with AD has suggested the use of antioxidants as promising therapeutic agents for treating AD [51–54]. However, clinical trials involving antioxidants have failed to elicit the desired anti-AD effects, possibly due to inefficient delivery. Nanotechnology-based approaches provide the much needed solution to this problem by offering effective drug/antioxidant delivery systems for targeting areas, which are inaccessible to other delivery methods. Research has further advanced in this area with the demonstration that antioxidants can pass through the BBB with the help of nanostructures.

Magnetic NPs (MNPs) possesses an excellent biocompatible contrast platform to target magnetic resonance imaging (MRI). Superparamagnetism coupled with lack of permanent magnetization at room temperature and excellent colloidal stability makes them highly suitable for both localized and systemic delivery via blood stream and nasal pathways. These properties of MNPs were exploited for developing high contrast probe for targeting amyloid beta oligomers (AβO) by Viola *et al.* [55▪]. The synthesized mono-dispersed nitro-dopamine (nDOPA) and polyethylene glycol (PEG) stabilized MNPs and modify their surface by carboxylation for obtaining efficient conjugation to AβO-specific antibodies. Antibody conjugated to surface modified MNPs could detect AD causing toxic oligomers on nerve cell surfaces in *in vitro* situation. They quickly reach oligomers *in vivo*, in a mouse model, following intranasal delivery. Prototype imaging of the mouse model and isolated human brain tissue substantiates the clinical potential of MRI of synaptotoxic oligomers using targeted nanostructure probes. In vivo, the probe reaches the brain following intranasal inoculation of mice and can provide an MRI signal that requires transgene-dependent AD study. It can be concluded that the development of humanized AβO-specific antibodies is expected to increase the potential of this approach for use in AD diagnostics and for measuring the efficacy of new drugs which are currently under clinical investigation. Nanotechnology-based probes which can be readily adapted to other targets may provide a strategic and powerful early detection advantage over current PET probes for amyloid by targeting AβOs which are responsible for damaging neuron early in AD.

In another approach, the autocatalytic generation of amyloid fibrils was explored by computer mediated simulations to identify the requirements needed for the self-replication of fibrillar assemblies of proteins in AD [56]. This physical approach reveals that self-replication occurred only in a very narrow regime of inter-protein interactions, implying a high level of sensitivity to system parameters and experimental conditions. The quantitative relation between the kinetics of self-replication and the surface coverage of fibrils by monomeric proteins revealed that some fundamental physical requirements are a must for forming supra-molecular structures which enables them to replicate themselves, and form the basis of amyloid formation in AD [56].

LIMITATIONS OF NANOTECHNOLOGY BASED ALZHEIMER'S DISEASE THERAPY

Research undertaken so far to transport drugs via nanocarriers across the BBB, while considerable, has certainly not enough and has not met expectations. considerable future effort is needed to make these NPs a viable solution for successful pharmaceutical purposes. Three approaches can be pursued from here onwards: i) to design intelligent NPs in such a way to incorporate various functionalization ligands that can bind the neuropharmaceuticals drugs in greater amount, and enhance their permeability across the BBB in a more effective manner; ii) to target more vigorously the *in vitro* imaging of AD; and iii) to construct nanobiosensors having accurate sensitivity for identifying cases early in the pathway to AD.

CONCLUSION AND FUTURE PERSPECTIVES

Nanotechnology-based approaches can provide a much needed foundation to develop application-specific drug delivery vehicles to treat various neurodegenerative disorders including AD. This can be achieved by preparing NPs in a systematic manner by combining disciplines such as nanomanufacturing, drug discovery and molecular biology/medicine, which will serve collaborative roles in the downstream realization of clinical NPs. Studies have shown that the surface of NPs can be modified by several functional groups via covalent and noncovalent methods for imparting extra stability and drug binding affinity to them. Hence, in the near future, NPs based drug delivery systems can provide hope for effective treatment of aggressive neurological disorders and treating resistant diseases in general. The progress in the development of a number of methods of NP functionalization with different kinds of drugs will definitely open possibilities to apply constructed systems of not only drugs but also gene and protein delivery. Moreover, continuous research on NPs is needed to seek further development including magnetism and nonlinear optical properties (optical trapping) in NPs so that they can be successfully employed for bioimaging, labeling and drug delivery systems. These properties will aid in successful validation of bioimaging, labeling and drug delivery tracing using NPs for future biomedical applications.

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Conflicts of interest

There no conflict of interest.

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- ■ of special interest
- ■■ of outstanding interest

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