

# Nanotechnology Building Blocks for Intervention with Alzheimer's Disease Pathology: Implications in Disease Modifying Strategies

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## Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder manifested by progressive loss of memory followed by irreversible dementia [1-3]. AD neurodegeneration is characterized by the loss of neurons preceded by cell membrane and cytoskeleton damage due to a complex of molecular pathways that finally lead to formation of amyloid- $\beta$  (A $\beta$ ) plaques and neurofibrillary tangles in the brain tissue [1-3].

Current treatments of AD can only partially alleviate symptoms, but there exists no cure to stop or slow neurodegeneration. The first major class of drugs used to treat AD was cholinesterase inhibitors which inhibit the proper functioning of the enzyme that breaks down acetylcholine. These drugs maintain a higher level of acetylcholine in the synaptic cleft thereby promote signaling and improve neuronal function; however, they do not prevent the underlying neurodegeneration [1-3]. On the other hand, all current disease-modifying strategies targeting different molecular pathways involved in AD have failed in phase 3 clinical trials [4].

As reported in our recent detailed studies [2,3], major molecular pathways involved in AD can potentially be targeted through nanotechnology methods [5] and molecular building blocks (MBBs) [6] as it is shown in Figure 1. In summary, the current and envisioned applications of nanotechnology in neurology consist of neuroprotection, neuroregeneration and drug delivery beyond the blood brain barrier (BBB).

Among the above-mentioned applications, nanotechnology neuroprotective approaches can be of great implication in effective disease-modifying strategies for AD, especially when the targeted molecular pathways are involved in more initial phases of AD pathogenesis. This report is focused on such neuroprotective approaches through nanotechnology molecular building blocks (MBBs). To this end, we first elaborate on molecular pathways of Alzheimer's disease targeted by each group of nanotechnology MBBs.

## Protection against Glutamate Excitotoxicity

A major pathological event in AD is synaptic failure [9], characterized by excessive synaptic release of glutamate and/or impairment of glutamate clearance mechanisms in the synaptic cleft. Glutamate together with D-serine are the primary excitatory neurotransmitters in the brain that activate voltage-dependent calcium channels through the N-methyl-D-aspartate (NMDA) receptors. Excessive synaptic glutamate, in turn, leads to a disruptive influx of calcium ions causing an overabundance of intracellular calcium, triggering several damaging pathways in neurons, and ultimately neuronal death (Figure 2) [1,5,6]. Therefore, a disease modifying approach against AD synaptic pathology could be preventing the excessive glutamate signaling by blocking the NMDA-receptor channels [5].

From the structural point of view, NMDA receptors are co-assemblies of different receptor subunits from different subunit

families: NR1 and NR2 as shown in Figure 3. Among these subunits, NR1 has the essential role in NMDA receptor function [8]. Co-assembly of different members of the above mentioned subunit families leads to composition of different NMDA receptor subtypes with discrepant biophysical and pharmacological properties [9]. A variety of binding sites for ligands exist in the structure of NMDA. These ligand/binding site interactions are almost subunit selective and result in regulation of NMDA receptor function [9] as shown in Figure 3.

The topologies of NMDA receptor subunits are almost the same. Each subunit consists of an extracellular N-terminal domain, four membrane (M 1-4) domains and an intracellular carboxyl terminal [8,9]. The extracellular domain (N-terminal) forms the glycosylated large part of each subunit, responsible for binding with ligands. Among agonist ligands, glycine binds to NR1 and glutamate binds to NR2 binding sites. The first and second intra-membranous domains are interconnected through an intramembrane loop. The M2 domain forms the receptor channel pore. The intracellular domain (carboxyl terminal) contributes to regulation of the receptor through second messenger system [8,9].

As discussed before, if excessive NMDA signaling is not controlled, a high influx of calcium leads to the impairment of mitochondrial function, cellular energy failure and finally neurodegeneration [5]. Previously developed drugs which act as NMDA antagonists were discontinued due to blocking the normal NMDA signaling, a process that can also promote neurodegeneration [5]. Selective blockade of the excessive NMDA signaling is possible through optimization of NMDA receptor partial antagonism via nanotechnology molecular building blocks (MBBs) and their derivatives [9,10].

A derivative of nanotechnology building blocks diamondoids, known as Memantine, shows effective partial NMDA receptor antagonism [6]. Memantine is a derivative of adamantane (1-amino-3,5-dimethyladamantane) the smallest diamondoid molecule [10] (Figure 4). Diamondoids are cage-like saturated hydrocarbons and one of the promising nanotechnology MBBs for biological applications. Memantine acts as a low-affinity and noncompetitive receptor antagonist which unbinds following strong synaptic activation due to its voltage-dependency and fast unblocking kinetics. Therefore, Memantine prevents excessive glutamate from setting off too high a calcium influx, while still allowing normal NMDA receptor to function

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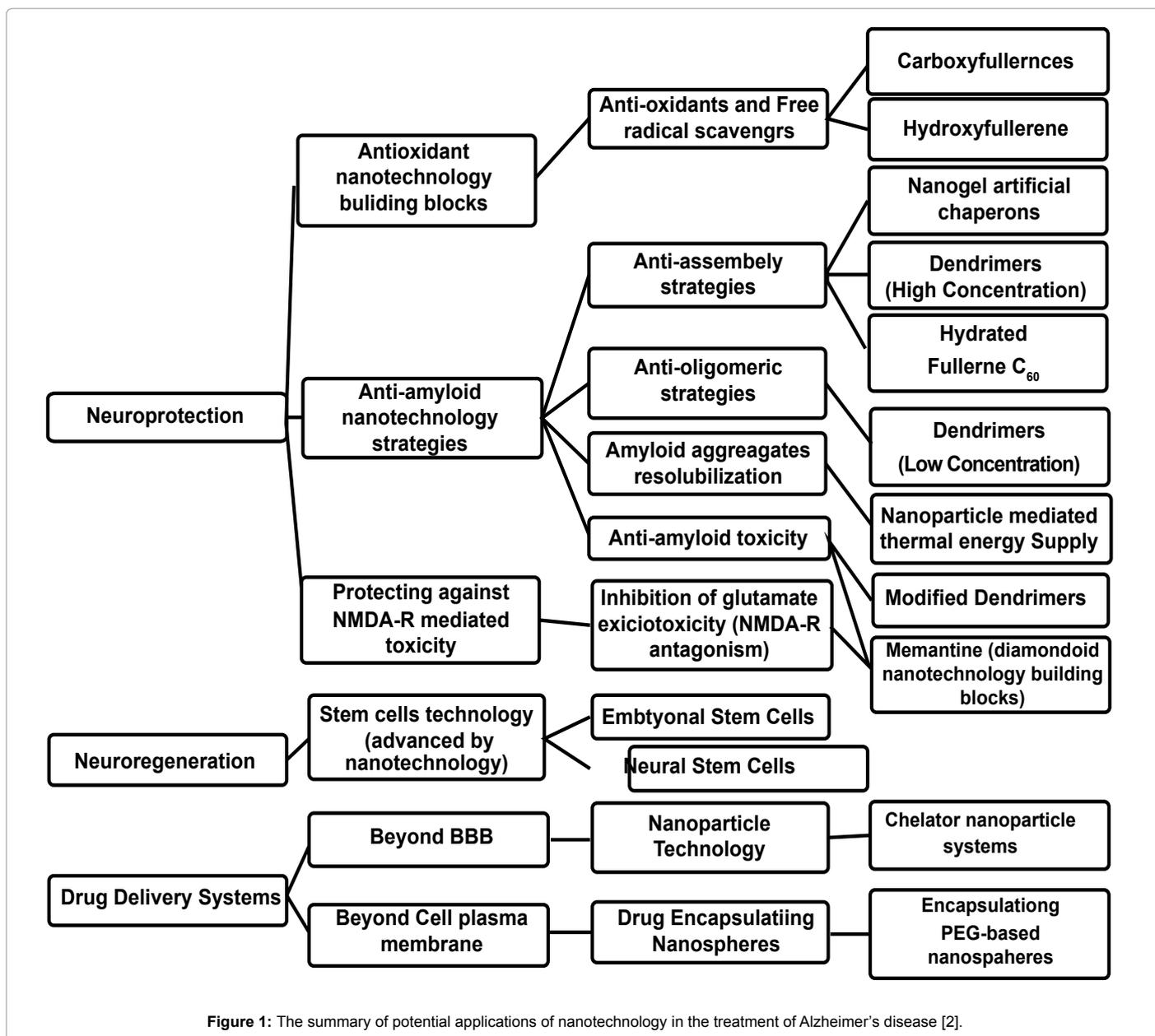


Figure 1: The summary of potential applications of nanotechnology in the treatment of Alzheimer's disease [2].

at normal concentrations of glutamate [5]. Memantine has become of great interest to researchers owing to such self-regulated mechanism that controls the amount of NMDA activation [11].

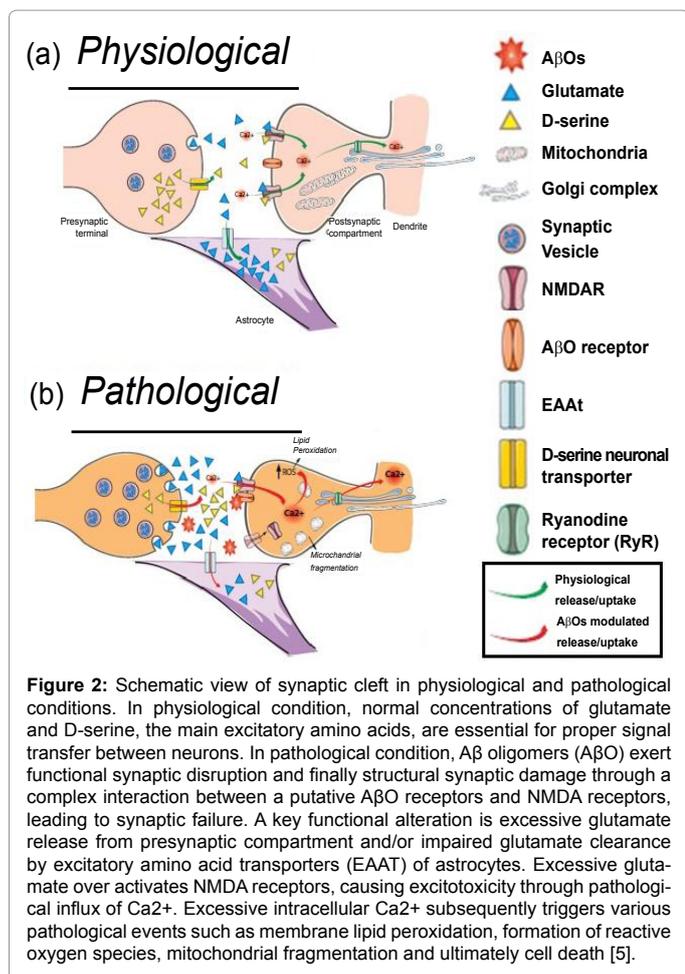
### Protection against Oxidative Stress

There is compelling evidence on initial role of mitochondrial derived oxidative stress in AD pathogenesis [12]. Mitochondria are crucial organelles to the eukaryotic cells for both energy generation and regulation of programmed cellular death (apoptosis). During the cellular energy metabolism in the mitochondria, semi reduced oxygen species (ROS), including super oxide and hydrogen peroxide, are normally produced [13]. According to the AD mitochondrial cascade hypothesis [14], during aging, which is the main risk factor for sporadic AD, the continual damage to mitochondrial DNA (mtDNA) leads to the malfunction of proteins of mitochondrial electron transfer chain

(ETC) [12-14]. The resultant decrease in ETC efficiency per se causes overproduction of ROS [13].

Oxidative stress happens when the production of ROS exceeds their neutralization. The ROS, unless neutralized, can contribute to some cytopathological reactions, including oxidation of mitochondrial DNA (mtDNA) and to a lesser degree nuclear DNA, as well as protein oxidation and lipid peroxidation. These pathological reactions, in turn, lead to cell death and degeneration [12-14]. It is noteworthy that, in addition to mitochondrial dysfunction, the interaction between toxic A $\beta$  aggregates and cell membrane is another major source of oxidative stress in AD pathology.

Fullerene is one of the main nanotechnology building blocks with strong antioxidant and free radical scavenger properties, owing to its specific chemical structure that allows it to be linked (i.e. functionalized)



to several active chemical groups in a 3-dimensional orientation [15-17]. Fullerene molecule is composed of a three-dimensional array of carbon atoms, evenly spaced in a pattern similar to rhombuses on a soccer ball [15-17].

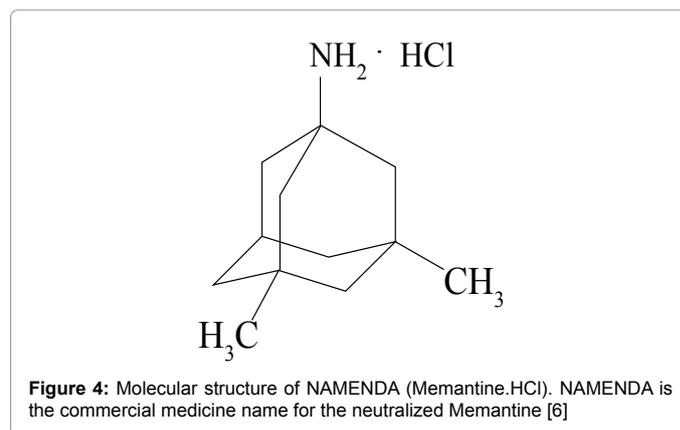
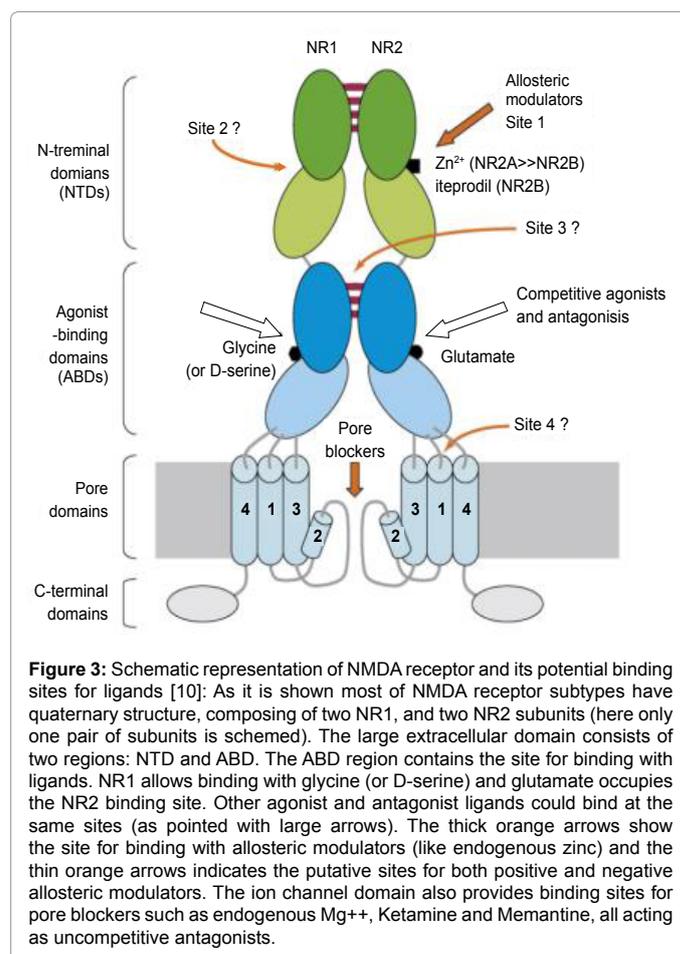
*In vitro* studies on Fullerenol, a water-soluble hydroxyl-functionalized derivative of fullerene, have shown neuroprotective properties against Aβ<sub>42</sub> via both antioxidant reactions and inhibition of Aβ<sub>42</sub>-induced Ca<sup>2+</sup> neurotoxicity [17]. Likewise, carboxy fullerenes (malonic acid derivative of C<sub>60</sub>, {C<sub>63</sub>[(COOH)<sub>2</sub>]<sub>3</sub>}) protect cultured cortical neurons from Aβ<sub>42</sub> induced oxidative stress and neurotoxicity [18]. Interestingly, the application of carboxy fullerenes blocked the Aβ<sub>42</sub> induced neuronal apoptotic death as well [18].

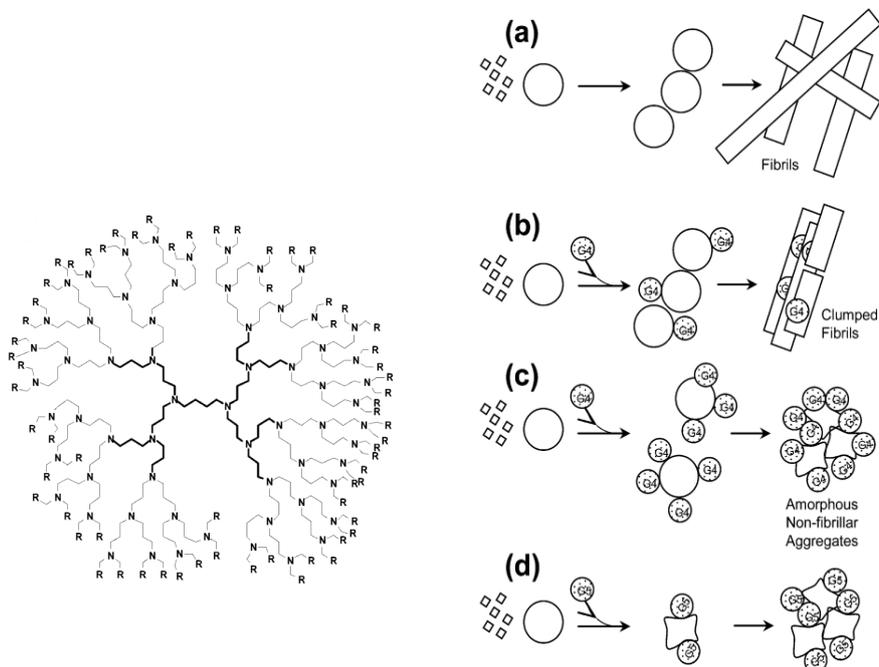
In addition, hydrated C<sub>60</sub> fullerene (C<sub>60</sub>HyFn) is shown to protect neurons against Aβ induced neurodegeneration *in vivo*, presumably owing to both its anti-oxidant and anti-amyloid properties [19]. The molecular mechanism of C<sub>60</sub>HyFn anti-amyloid properties is not clear yet [19]. Anti-amyloid properties were also attributed to sodium fullerenolate Na<sub>4</sub>[C<sub>60</sub>(OH)<sub>~30</sub>] (NaFL), a water soluble poly-hydroxylated fullerene derivative [20]. NaFL destroys mature amyloid fibrils and at the same time prevents from Aβ aggregation and fibril formation. Thus, increased concentration of Aβ oligomers due to Aβ fibril break-down might be a source of potential toxicity *in vivo*. Of course, *in vitro* studies reported NaFL toxicity is exceptionally low. However, this is to be confirmed in pre-clinical *in vivo* trials [20].

## Protection against Amyloid-β induced Synaptic and Neuronal Damage

In early stages of AD, symptoms are more due to Amyloid-β (Aβ) damage to synapses rather than its damage to neurons themselves. For example, the early memory impairment is more related to Aβ synaptotoxicity than its neurotoxicity [21]. Therefore, the synaptic degeneration and its presentations in early clinical symptoms of AD precede neuronal degeneration and death [22,23].

Growing evidence suggests the culprit molecules in synaptic





**Figure 5** Structure and function of PPI-Mal dendrimers. **(a)** Chemical structure of PPI-G4-Mal dendrimer. **(b)** Schematic representation of different dendrimer-amyloid interactions, and morphology of the resulting aggregated species **(a)** Polymerization process of A $\beta$ (1-40): monomeric peptide ( $\diamond$ ) assembles as peptide oligomers (O); peptide oligomers combine into prefibrillar structure (OOO) and eventually convert into fibrils ( $\square\square$ ). **(b)** At low dendrimer-peptide ratios, the interaction of the PPI-G4-Mal dendrimer with the monomeric peptide does not prevent the fibrillization, but clumps fibrils. **(c)** At high dendrimer-peptide ratios, PPI-G4-Mal prevents the fibrillization, leading to the formation of dendrimer-peptide oligomer complexes. These complexes combine in the form of granular nonfibrillar amorphous aggregates. **(d)** PPI-G5-Mal changes the peptide oligomeric structures, probably through formation of a higher number of hydrogen bonds per dendrimer (even at low dendrimer-peptide ratios), thus preventing the fibrillization and leading to the formation of amorphous aggregates [36].

degeneration are the soluble oligomeric species of A $\beta$  (A $\beta$ O), and the process is independent of the levels of amyloid precursor protein (APP) expression, A $\beta$  monomers and amyloid depositions [22,23]. The exact downstream mechanisms of A $\beta$ O on synaptic degeneration are not clear yet. However, postsynaptic terminals are shown to be more affected than pre-synaptic terminals in A $\beta$ O induced toxicity (Figure 2) [5]. Interestingly, A $\beta$ O induced synaptic disruptions are more functional in the beginning, and are followed by structural disruptions later in the disease process. The functional synaptic impairment mainly include a reversible disruption in long term potentiation [24,25].

Some signaling pathways have been suggested to account for the functional toxic effects of A $\beta$ O. The backbone of these pathways is a putative synaptic terminal receptor with high affinity to A $\beta$ O, which is not yet fully characterized [5,25]. However, there is strong supporting evidence regarding association of A $\beta$ O with some synaptic terminal receptors, including Fyn, Arc, glutamate receptors and PSD 95 protein. It is hypothesized that specific interactions of A $\beta$ O with PSD-95 protein lead to a displacement of Fyn, which is tethered by PSD-95 protein to the signaling chain [26]. Displacement of Fyn receptor will then inhibit the c-AMP response element-binding (CREB) protein signaling ending in synaptic dysfunction and eventually neuronal death [26].

Not only the extracellular A $\beta$ O, but also the intra-membranous and intracellular A $\beta$ O can have toxic effects on synaptic terminals. We have discussed the intra-membranous oligomerization of A $\beta$  and its subsequent permeabilization effect on the plasma membrane as a neurotoxic mechanism elsewhere [2,3]. In addition to the same intra-membranous oligomerization mechanism, intracellular A $\beta$

oligomerization is proposed as a mechanism for synaptic degeneration following intra terminal accumulation of A $\beta$  [27].

A $\beta$ -synaptotoxicity may also occur through localized apoptotic changes as evidenced by caspase activation in neurites [28]. Caspase is the name for a family of cysteine proteases that are responsible for regulating apoptosis in mammalian cells. However, it is not completely proven whether the activation of caspases in AD causes classic apoptotic effects or if it merely performs some apoptosis-associated molecular dysfunctions in the neurons [28]. Some caspases, especially caspase-6, have been recently suggested as the first molecular responses of the insulted neurons and as triggers for further disruptions in the structure of neuronal cytoskeleton and subsequently in the neuronal trafficking [28,29].

Blocking toxicity of A $\beta$ O has been widely studied as a disease modifying strategy for AD. To date, dendrimers are one of most validated nanotechnology designed structures with anti-amyloid properties [34]. Dendrimers are highly branched macromolecular structures with globular shape (Figure 5) and a densely packed surface [30-34]. Beside their potent anti-amyloid effects, however, most dendrimeric structures exert cytotoxic effects on neurons. Therefore, designing dendrimers with minimal toxicity has been the focus of several recent studies. Recently, minimally toxic dendrimers like poly-L lysine dendrimers D3 and D5 were found with strong anti-amyloid properties as demonstrated in human neuroblastoma SH-SY5Y cells. In addition, D3 lysine dendrimers, attenuated A $\beta$  induced increases in K<sup>+</sup> channel current [35]. Interestingly, following intraventricular injection

of fluorescence-labelled D3 dendrimers to rat brain, dendrimers were found distributed to both parietal cortex and hippocampus, major regions involved in AD, without any sign of cell death throughout the brain [35].

Similarly, maltose (Mal) decorated glycodendrimers, poly(propyleneimine) (PPI) dendrimers have also shown minimal toxicity in vitro [36]. Among them, specifically fourth (PPI-G4-Mal) and fifth (PPI-G5-Mal) generation glycodendrimers interfere with amyloid peptide A $\beta$  (1-40) fibrillization in a generation dependent manner: PPI-G5-Mal blocks amyloid fibril formation and PPI-G4-Mal clumps fibrils together (Figure 5) [36]. Blockade of amyloid fibril formation through PPI-G5-Mal leads to generation of granular non-fibrillar amorphous aggregates (Figure 5B). Likewise, PPI-G4-Mal fibril clumping leads to amorphous aggregates at high dendrimer-peptide ratios, but clumped fibrils at low ratios (Figure 5B). Fibril clumping reduces amyloid toxicity whereas amorphous aggregates are toxic to cells [36]. Of course, no cellular toxicity was found due to PPI-G4-Mal or PPI-G5-Mal themselves [36]. Further studies on in vivo effects of glycodendrimers are required to test their biocompatibility as anti-amyloidogenic compounds for AD [36].

Interestingly, in a recent study, cationic phosphorus-containing dendrimers (CPD) (generations 3 and 4) were proved capable of interfering with both A $\beta$  and MAP-Tau aggregation processes [37]. In this study, the fragment of amyloid peptide (A $\beta_{1-28}$ ), which is the core region responsible for aggregation, was used as a model for full-length A $\beta$  monomer [37]. The cytotoxicity associated with formed fibrils and intermediate products of A $\beta_{1-28}$  aggregation decreased in the presence of CPDs via regulation of the fibrillization process [37].

Generally, dendrimers regulate A $\beta$  fibrillization in a concentration dependent manner. In low concentrations, dendrimers facilitate A $\beta$  fibrillization, whereas in higher concentrations, they block A $\beta$  fibrillization [33,34], either via their binding with peptide monomers or through blocking the end of protofibrils and fibrils [34]. The therapeutic importance of this dualistic behavior of dendrimers is rooted in the recently described protective, rather than toxic role of A $\beta$  fibrillization. Based on this paradigm, A $\beta$  fibrillization is a natural mechanism to neutralize the toxic A $\beta$ Os, which can be considered as an alternative way to compensate for the impaired A $\beta$  clearance mechanisms in AD brain. In this regard, lower concentration of dendrimers could contribute to disease modification of AD through neutralizing toxic A $\beta$ Os via enhancement of A $\beta$  fibrillization [33,34]. An exception may be gallic acid-triethylene glycol dendrimer decorated with 27 terminal morpholine groups ([G3]-Mor) that facilitate amyloid fibrillization in high concentrations [38]. Interestingly, in line with the abovementioned notion, the results of G3-Mor and A $\beta$  interaction showed concomitant increase in A $\beta$  fibril formation and decrease in A $\beta$ -induced toxicity [38].

## Conclusions

Thus far, all disease modifying strategies designed to slow or halt the Alzheimer's disease molecular pathogenesis have failed in phase-3 clinical trials [4]. Future perspective on finding a cure for AD is not bright, without any considerable shift in the paradigms explaining the underlying mechanisms of AD, establishing and validating relevant animal models used in preclinical studies [39] and methodologies used in drug design and discovery. While toxic side effects are still the major concern about different nanoparticles, biochemical features of these particles show potentials of a methodological breakthrough in targeted

drug delivery to specific molecules involved in AD pathogenesis.

Recently, disease modifying potentials have been suggested with Memantine [40,41], a derivative of adamantane the smallest diamondoid molecule [42,43]. Diamondoids are key molecular building blocks for nanotechnology with several biological implications [44], including NMDA receptor antagonism as shown in NAMENDA. Clinically, NAMENDA is beneficial for treatment of moderate to severe AD.

As the currently dominant paradigm of AD pathogenesis emphasizes on A $\beta$  induced toxicity, several nanotechnology building blocks have shown neuroprotective effects against different mechanisms through which A $\beta$  damages neurons. For instance, A $\beta$  damage to synapses and neuronal cell membrane could be restrained via anti-amyloid (e.g. dendrimers) and anti-oxidant (e.g. fullerenes) nanotechnology building blocks respectively.

It is noteworthy that beside efforts towards effective disease modifying agents for AD, nanotechnology research is also focusing on drug delivery systems that can allow targeted delivery of both current symptomatic and envisioned disease-modifying agents to the brain [2,45], thus providing higher efficacy with minimal toxicity.

In conclusion, nanotechnology can provide potent agents to modify the course of certain pathological mechanisms involved in AD. However, translation of these strategies to actual modification of Alzheimer's disease course in human subjects lies largely not only on biocompatibility of these agents, but also on the accuracy of our current paradigms about molecular mechanisms underlying AD [46].

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