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REVIEW ARTICLE

Alzheimer's Disease – Future Therapy Based on Dendrimers

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Abstract: Alzheimer's disease (AD) is characterized by the loss of neurons. It is the most common cause of dementia in the elderly population accompanied by pathological degeneration of neurofibrillary tangles. Senile plaques are formed with beta-amyloid, hyperphosphoryled tau protein, apolipoprotein E and presenilin associated with protease activity [amyloid beta (Aβ), gamma-secretase (γS)]. The molecular mechanisms of neurodegeneration include apoptosis, oxidative stress (free radical generation), inflammation, immune activation, and others. The lack of effective treatments for AD stems mainly from the incomplete understanding the causes of AD. Currently, there are several hypotheses explaining the early mechanisms of AD pathogenesis. Recent years witnessed an unprecedented research growth in the area of nanotechnology, which uses atomic, molecular and macromolecular methods to create products in microscale (nanoscale) dimensions. In this article, we have discussed the role of nanotechnology in the development and improvement of techniques for early diagnosis and effective treatment of AD. Since AD pathology is practically irreversible, applications of disease-modifying treatments could be successful only if early diagnosis of AD is available. This review highlights various possibilities for the early diagnosis and therapy of AD and investigates potential adaptation of nanoparticles-dendrimers as a class of well-defined branched polymers that are chemically synthesized with a well-defined shape, size and nanoscopic physicochemical properties reminiscent of the proteins for the treatment of neurodegenerative diseases.

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1. INTRODUCTION

Alzheimer's disease (AD) is a progressive degenerative disease that occurs due to the loss of primary mental functions. It is undoubtedly an important medical problem with considerable social repercussions and requires exemplary attention. Nanotechnology and nanomedicine provide a new and interesting direction of development of new methods and materials that could be potentially used in the treatment of many diseases, including neurodegenerative disorders [1]. Dendrimers (derived from the Greek word '*dendron'* meaning *'a tree'*) are large and diverse group of nanomolecules known for decades [2]. Two independent research groups previously reported dendrimer synthesis. Donald Tomalia [3], Fritz Vögtle [4] and George F. Newkome [5] initially called their products 'arborolami' (derived from the Latin word *'arbor'* meaning *'a tree'*). Initially, the nanomolecules were synthesized by the divergent method, which in the case of polyamidoamine dendrimers (PAMAM) included an addition of monomer layers to a multifunctional core. According to chemistry reactions, it was a sequence of Michael's addition [6]. However, during the synthesis reaction, this method encountered a problem in the form of very dense terminal

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functional groups, often causing the formation of molecules of different defective structures. Hence, it was decided to change the synthesis method of dendrimers. The new alternative was proposed by Frechet *et al*. which was called the 'convergent method'. It consists of two steps: a branch is synthesized in the first step, and then a branch reacts with the core in the second step. This approach enables better control of process efficiency and purity of the final product [7].

Dendrimers are spherical or disk-shaped structures, monodisperse, and have a lower viscosity than their linear polymer equivalents [8]. The presence of a large number of hydrophilic functional groups on the surface of the molecule results in better solubility of the nanostructures in water resulting in high reactivity when required for the surface modification [9]. According to the type of surface groups for the dendrimers, PAMAM adopts to mark out a complete generation of nanomolecules. In one method, the surface of the dendrimers have amine groups ($-NH_2$) or hydroxyl groups (-OH). In another method, carboxyl groups (-COOH) which are suitable anionic structures are present on the surface of dendrimers [10].

The interest in these nanostructures and the possibility of their potential use in medicine has led to the preparation of chemically diverse organic and inorganic dendritic branched molecules. The best known and most commonly used in biological research are polyamidoamine (PAMAM) and polypropyleneimine (PPI) dendrimers. Each dendrimer is composed of a core with symmetrical branched arms called dendrons diverging radially. Among them, there are the spaces ("cavities") which are used to store different kinds of molecules with a hydrophobic, hydrophilic, and amphiphilic properties. The resulting structure of the dendrimer contains both hydrophilic and hydrophobic interior surfaces making up the nanomolecules that could potentially act as carriers of various substances including many chemotherapeutic agents (Fig. **1**).

Active compounds could be enclosed in the hydrophobic cavities between dendrons (encapsulations) [11] and/or covalently bound to the surface groups. It was shown that binding of biologically active compounds to the dendrimer increases its therapeutic activity in comparison to an equivalent amount of the free substance. This is called the "dendritic effect" [12]. Dendrimer and its conjugates with many active substances could easily pass through the cell membranes causing an increase in the bioavailability of the chemotherapeutic agent. Esfand and colleagues reported the hydrolysis of a covalent bond and the release of the active compound at a particular location in the body. This effect is crucial for achieving reduced systemic toxicity of the drug [13].

In addition to the cancer therapy where dendrimer transports the selected chemotherapeutic agent and subsequently controlling its release in the environment of the tumor *via* the presence of the pH-sensitive binding of the dendrimer-drug complex [14], a new feature of these molecules was investigated in the treatment of photodynamic therapy (PDT). The ability of dendrimers to the electrostatic binding of different type and origin of nucleic acids and forming complex dendrimer-DNA [15], dendrimer-RNA [16] increasing the efficiency of transport of acid to the cell and avoiding degradation of both in the extracellular space and enzymatic degradation in the cytoplasm that indicates expansion of the experimental approaches to study the molecular requirements

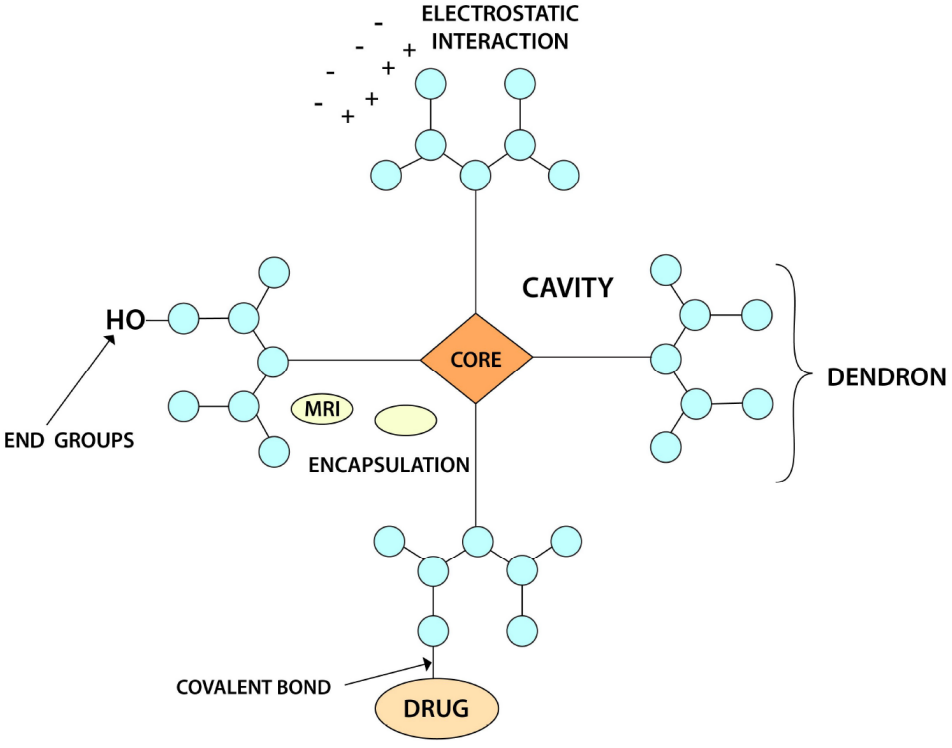

Fig. (1). Schematic diagram of the dendrimer and the types of interactions with transported substances. (*The color version of the figure is available in the electronic copy of the article*).

of the interaction of RNA-based therapeutics and PAMAM dendrimers of different generations. Hence, dendrimers could be potentially used in gene therapy.

Another promising application in research involves the use of the nanomolecules in the diagnosis using Magnetic Resonance Imaging (MRI). Dendrimers act as carriers for contrast producing a substantial reduction in the relaxation time of paramagnetic particles [17]. Dendrimers and their metal complexes also exhibit antimicrobial [18] and antivirus activities [19].

The use of dendrimers is limited due to their toxicity which is associated with the hemolytic activity of nanomolecules. The increase in cytotoxicity both depends on the generation of the dendrimer and the functional groups on the surface of nanomolecules. To reduce the toxicity of nanomolecules, they are coated with various substances such as fatty acids, lipids, and other types of biologically safe polymers, *i.e*. poly(oxyethylene) PEG [20].

2. NEUROBIOLOGY AND PATHOGENESIS OF ALZHEIMER'S DISEASE

The histological criterion of AD involves the formation of neurofibrillary tangles (NFT) in the intraneuronal structures and neuropil threads (NT). The first changes in the brain are observed in the hippocampus, amygdala, thalamus, forebrain, and numerous monoaminergic brainstem nuclei. Some parts of the brain such as cerebellum are intact even in the advanced phases of the disease [21]. The pre-clinical stage could last for many years while the limbic system is gradually degraded. As a result, neurons are loaded with depositions of lipofuscin and melanin pigments which are particularly sensitive to changes in the cell cytoskeleton. Precipitation of the insoluble extracellular Aβ serves as the center of the senile plaques which are unevenly distributed in the brain, whereas amyloid deposits typically occur later than intraneuronal changes. Least of all are occurring in the hippocampus, and the most are in the temporal and occipital cortex. The accumulation of plaques in the brain begins at about 50-th year in patients and increases gradually in subsequent years. The accumulation of senile plaques in AD compared with the normal aging brain is characterized by a higher concentration of soluble and insoluble Aβ-42, more modifications of terminal amino acids of Aβ and Aβ-40-42 as well as the increase of their concentration. The very slow process of accumulation of Aβ deposition promotes the formation of pathological modifications of the peptide such as racemization, isomerization, cyclization, and oligomerization leading to the insolubility of Aβ-42 [22].

There are several linked abnormalities in many systems of neurotransmission in AD such as in cholinergic, noradrenergic, and dopaminergic systems. Mainly, adenylyl cyclase, phosphoinositides and protein kinase C are among disturbed components of the signal transduction pathways. Pathological changes in the concentration of free calcium release and retrieval, in a cascade of phosphatidylinositol, protein kinase C, and in a level and biosynthesis of cyclic adenosine monophosphate (cAMP) occur in fibroblasts of patients with AD. Such changes in signals transmitter leads to changes of aerobic metabolism and treatment of amyloid protein as well as tau protein phosphorylation [23].

Initially, an inflammation hypothesis was considered the main factor in AD and it was verified based on the self-destructive changes associated after the death of patients and epidemiological evidence on the protective effect of anti-inflammatory agents. It is known now that the local acute phase response occurs in the brain, and the risk of AD affects many biologically active compounds. Activated microglial cells, macrophages/monocytes are important components of the inflammatory response of the central nervous system (CNS), mainly in regions of amyloid deposits of Aβ-39-43. Senile plaques are characterized by a self-sustaining inflammation without the classic acute phase, meanwhile activating the pathway of complement C1q and cytokines involves acute phase proteins (C-reactive protein, heme oxygenase-1) [24]. Induction of inflammation may occur with the participation of extraneous antigens, but also by endogenous factors triggering the inflammatory response as proinflammatory cytokines, dead cells, amyloid protein deposits, including Aβ. Activation of glial cells (astrocytes and microglia) accelerates the removal of extraneous pathogens, damaged cells and the dead cells, phagocytosis and removal of amyloid deposits, including aggregates of Aβ. However, excessive glial activation leads to neurotoxic effects and accelerates the progression of neurodegeneration. One of the important factors inducing inflammation is the neurotoxic effect of amyloid oligomers. The toxic effects of amyloid proteins often lead to neuronal apoptosis or necrosis. Removal of dead cells is a potent stimulus activating glial cells (mostly microglia) in the CNS. Activated, in the presence of Aβ, microglial cells proliferate and migrate into the damaged or dead neurons removing them *via* phagocytosis while releasing glutamate and starting synthesis of a number of mediators of inflammation, including cytokines, complement components, nitrous oxide, oxidases dependent on NADPH, COX-2, and particles of MHC II. Undoubtedly, one of the important mechanisms of inflammation is the activation of the complement cascade. Within the amyloid plaques and NFT in the brains of patients with AD regularly found the presence of active components of the complement system. Complement components are increased in the brains of patients with progressing neurodegeneration. It is found that the increase of complement components, membrane attack complex: C5b-9 (MAC) in the senile plaques, which is a potent cytotoxic agent. MAC may increase neurotoxic effects of Aβ. However, the role of the active components of the complement system in the development of neurodegeneration is not clear. It was shown that some C3a and C5a act as neuroprotectors from excitotoxic effect of the over-stimulation of NMDA receptors [25]. Further research is required to establish the role of individual components of the complement system in various clinical stages of neurodegeneration.

Proinflammatory cytokines (TNF-alpha, IL-1beta, IL-6, IL-17) and products of arachidonic acid cascade promote the spread of inflammation in the brain. Therapeutic strategies designed to inhibit the biosynthesis and secretion of cytokines are developed intensively. The idea is to monitor the

synthesis and secretion of cytokines, and blocking the signal transduction pathways [26].

The common mechanism of action of oligomers and amyloid proteins is their physicochemical interaction with cell membrane leading to the increase in its permeability to various compounds, including Ca^{2+}. Various type of oligomers such as alpha-synuclein, Aβ polyglutamine proteins, PrPsc, transthyretin and other proteins forming units increase the electrical conductivity of the lipid bilayer of cell membranes. The monomers and fibrillar aggregates of these proteins do not have such an effect. These effects depend on the concentration of oligomers but do not depend on the primary structure and amino acid sequences. The same interact with lipid membranes of cells described for oligomers of different amyloid proteins, because they have similar tertiary structural/spatial conformation. After removal and/or binding oligomers membrane pattern of the sible return back to the primary position [25].

The increase in the permeability of cell membranes as a result of the interaction of Aβ with the lipids leads to different types of effects with the most impact on the levels of intracellular Ca^{2+}. This mechanism in a significant degree impairs cell functions resulting in apoptosis of neurons. It appears that the increased membrane permeability is a universal feature of protein enriched in beta-sheet structures of various amyloidogenic proteins. Currently, most researchers believe that the increase in the influx of Ca^{2+} through ion channels and depolarization of the membrane of neurons are independent mechanisms of neurotoxic effect of Aβ. The effect on long-term postsynaptic potential stimulant is additive, but it can be separated through the use of selective inhibitors of mGluR1 and AMPA/kainate receptors [26].

The mechanisms of neurotoxicity of amyloid proteins depend on interaction with the components of cell membranes, including lipids, proteoglycans, and the receptor proteins. Recent studies show that these impacts are crucial in the development of neurodegeneration. The available data show various effects of Aβ on different neuronal and glial cell receptors affecting the lifespan and metabolism of neurons. The consequences of Aβ binding to lipoprotein receptors (the LDL receptor family) are among interactions of Aβ with membrane receptors that are relatively well understood. One of the most known LDL receptor is low-density-lipoprotein receptor-related protein 1 (LRP1) receptor. It plays an important role in the pathogenesis of neurodegeneration. LRP1 is the main receptor for lipoprotein ApoE in the brain. Cholesterol is internalized into neurons by endocytosis mediated by LRP1. Receptors of the LDL family also participate in the binding and internalization of amyloid precursor protein (APP). LRP1 reduces the secretion of α-APP and enhances the formation of amyloid beta due to increased endocytosis of the receptor. Another receptor in this family is ApoER2-increased expression of APP in the cell membrane, reduces its endocytosis and increases the formation of Aβ [27].

3. NEW LINES OF THERAPY-DENDRIMERS

Pharmacological treatments of AD are mainly based on symptomatic treatment, aimed at improving the psychosocial functioning of the patient and slowing down the disease process. It is aimed at reducing deterioration of cognitive function (*e.g*. memory, speech, attention, *etc*.), and the treatment of mental disorders and behavioral disturbances associated with dementia, for example, depression, agitation, and psychotic symptoms. It was observed that the granular non-fibrillar aggregates of Aβ (GNAs) are created on the surface of a biological membrane by destroying the two-layer structure leading to chronic inflammation and apoptosis. The growth kinetics of the process of creating GNAs are followed by the acidification of the environment outside of the cells as the result of the oxidation of lipids and/or hypoxia [28]. Aβ deposits impede the process of impulse conduction between cells altering the redox balance of the body, and activate the formation of reactive oxygen species induces inflammation. Aβ intermediate oligomers products are extremely toxic to neurons [29]. Due to the accumulation of so many different disturbances at the cellular level and changes in the physiology of the action, the search for effective treatment of AD is a challenge for modern neurobiology and nanomedicine.

Studies have shown that dendrimers PAMAM 3, 4, and 5 inhibit the formation of amyloid deposits. They exhibit hydrolytic properties relative to the existing forms of aggregated proteins. After incubation of cells with the dendrimers nano-molecules, there were no forms of Aβ resistant to hydrolysis. This observation indicates that the PAMAM dendrimers are not only inhibitors of amyloid aggregation, but also could remove the existing toxic forms of aggregated proteins [30]. Reducing the effective concentration of amyloid structures by the PAMAM dendrimers may take place in three ways: (a) dendrimers bind peptides, (b) locking of the free ends of the fibrils by increasing dendrimers, and (c) accelerating the dissolution of fibrils [30].

Studies have shown that the branched structure of dendrimers is essential for the effectiveness against Aβ aggregates. The cytotoxicity of Aβ depends on the degree of aggregation. It has been shown that the prefibrillar molds are much more cytotoxic than the mature fibrils. The solution to the problem of excessive formation of toxic forms of Aβ 1-28 in the cell could be catalyzing the process of aggregation and fibril formation. The gallic acid-triethylene glycol (GATA) dendrimers third-generation, modified by 27 molecules of morpholin, significantly reduces Aβ toxicity by lowering the number of prefibrillar forms and accelerating the formation of amyloid fibrils [31].

At the same time, it was observed that the dendrimers can modulate Aβ aggregation process if sugar groups are attached on the surface. The interaction between the PPI dendrimers of the fourth and fifth generations with the surface-modified groups of maltose and amyloid Aβ 1-40 was examined. As a result, PPI-G5-Mal inhibits the formation of granular and amorphous protein structures; whereas PPI-G4-Mal reducing the toxicity of amyloid with “clumping” fibril protein [32]. It was also found that the cationic phosphorus dendrimers (CPDs) effectively disrupt the thermodynamic equilibrium of formation of Aβ fibrils, and also the aggregation of other proteins [33]. Cationic phosphorus dendrimers proved to be useful for inhibiting the aggregation process of MAP-Tau which plays a role on sustaining the stability of

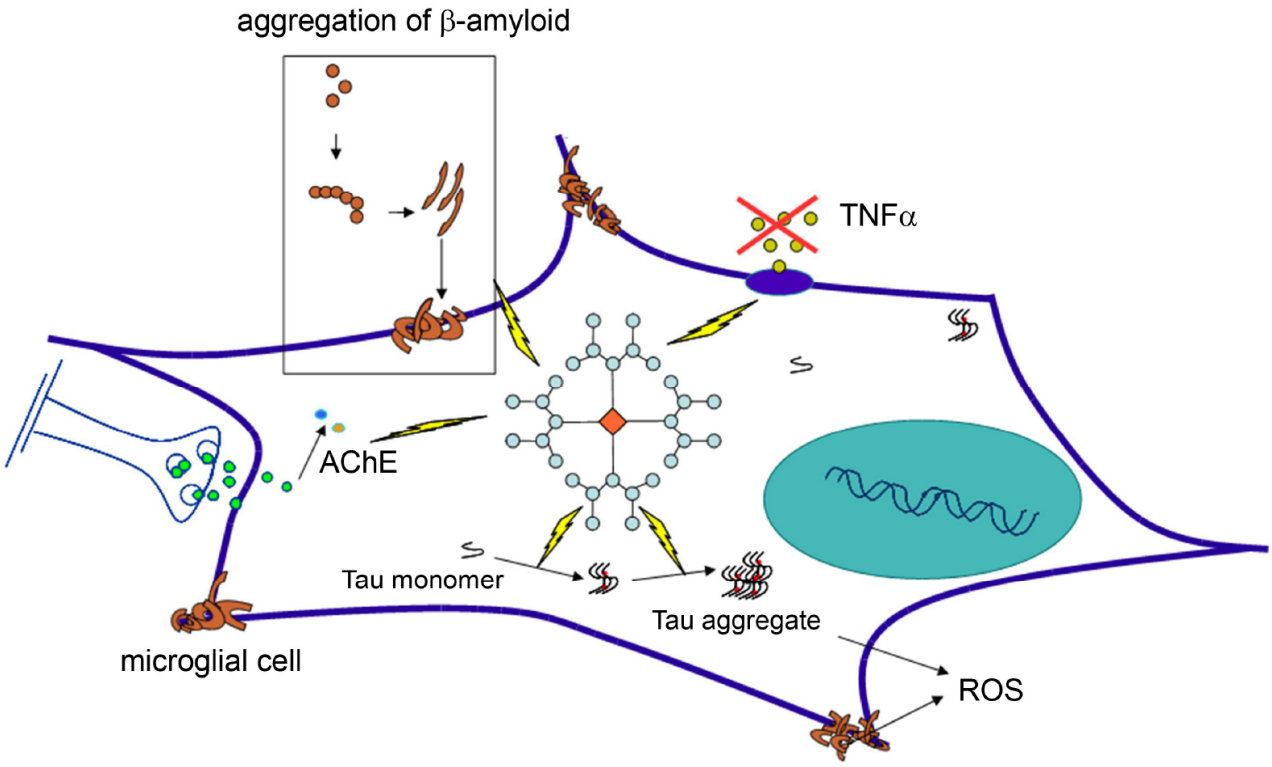

Fig. (2). Effect of cationic dendrimers of phosphate on pathological changes in microglia cell. (*The color version of the figure is available in the electronic copy of the article*).

microtubules while preserving the proper cell shape. Pathological aggregation is correlated with the hyperphosphorylation of MAP-Tau in neurons and glial cells. Phosphorylated protein is unable to bind to microtubules resulting in the loss of cell homeostasis and subsequent death [34-36]. It has been shown that CPDs suppress the aggregation of amyloidogenic proteins even at very low molar concentrations [37].

In addition to the formation of Aβ and MAP-Tau, the neurodegeneration process in AD patients is also associated with the activation of microglia cells, increased oxidative stress and a reduction in transduction of signals in cholinergic neurons. An ideal drug for AD should exhibit the anti-inflammatory properties, inhibit hydrolysis of acetylcholine, and "sweep" forming reactive oxygen species [38]. Cationic phosphorus dendrimers showed all these qualities. Poor antioxidant properties were observed at very low concentrations of the dendrimer. A similar reaction was observed with the secretion of TNF-α-cytokines, associated with the inflammatory process. It was noted that after incubation of cells with CPDs, TNF-α levels were comparable in the inactive microglial cells [39]. Effect of CPDS on the pathological changes in microglia cell caused by AD is shown in Fig. **2**.

The variety of pathological changes in neurons and glial cells, which act as a brake on dendrimers suggest that in the future they could be used in the treatment of neurodegenerative diseases. However, it is necessary to obtain dendrimers with adequate blood-brain barrier permeability. The solution to this problem lies in the use of polyester-co-polyether dendrimers (PEPE) synthesized by the Dhanikula team. Studies have shown that their structures have properties enabling them to overcome BBB penetration issues [40].

CONCLUSION

Finding effective agents to battle AD pathology represents a tough issue in current nanomedicine and medicinal chemistry. We have reviewed current advances on the use of potent polyamidoamine (PAMAM) and polypropyleneimine (PPI) dendrimers nanomacromolecules which could be used for the MRI diagnosis, site-specific drug delivery and gene therapy. However, many challenges still remain with potential cytotoxic effects and issues with blood-brain barrier permeability that requires further biochemical and molecular characterization of dendrimers. At this point, it is clear that novel compounds and materials are needed to attribute the multi-targeted pathology such as AD.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's disease
Aβ	=	Amyloid beta (Aβ) protein
APP	=	Amyloid Precursor Protein
cAMP	=	Cyclic adenosine monophosphate
CNS	=	Central nervous system
γS	=	Gamma-secretase
NFT	=	Neurofibrillary tangles
NT	=	Neuropil threads

PAMAM = Polyamidoamine

PDT = Photodynamic therapy

PPI = Polypropyleneimine

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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