DRUG DELIVERY SYSTEMS IN ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimers disease is a neurodegenerative disease characterized by the presence of amyloid plaques and taupathies in the brain, which is the cause of dementia. Currently only five drugs are approved by the FDA for the treatment of the Alzheimer's disease that too which only slow down the progression of disease and does not cure it. But however due to side effects of the drugs newer methods of delivery drugs are required. These drug delivery systems should be such that they can cross blood brain barrier and should efficiently deliver the drug to the brain. Hence various delivery systems are being studied which have still not reached the phase of clinical trials which shows how challenging is the development of the delivery system is in treat of Alzheimer's disease and with the rise in the number of patients suffering from Alzheimer's disease it becomes necessary for the pharmaceutical sector to develop patient friendly drug delivery system. Few systems being discussed are chemical drug delivery system, nanoparticles, transdermal patch, vaccines, and exosomes.

KEY WORDS: Alzheimer's disease, blood brain barrier, drug delivery systems.

INTRODUCTION

A neurodegenerative disease, Alzheimer's disease is histologically characterized by the presence of neurofibrillary tangles and amyloid plaques. It is diagnostically characterized by impaired cognitive function and loss of memory caused due to degeneration of the neurons in the hippocampal region (associated with memory). Initially, symptoms associated with alzhiemer's disease were considered associated with age related memory loss. Alzheimer's disease is a neurodegenerative disease characterized by the presence of amyloid plaques and taupathies in the brain which is the cause of dementia. Currently only five drugs are approved by the FDA for the treatment of the Alzheimer's disease that too which only slow down the progression of disease and does not cure it. But however due to side effects of the drugs newer methods of delivery drugs are required. These drug delivery systems should be such that they can cross blood brain barrier and should efficiently deliver the drug to the brain. Hence various delivery systems are

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being studied which have still not reached the phase of clinical trials which shows how challenging is the development of the delivery system is in treat of Alzheimer's disease and with the rise in the number of patients suffering from Alzheimer's disease it becomes necessary for the pharmaceutical sector to develop patient friendly drug delivery system.

Pathophysiology of Alzhiemer's disease (Rang and Dale, 2007)

The two important factors associated with pathophysiology of Alzheimer's disease are:

1. Extracellular amyloid plaques, consisting of amorphous extracellular deposits of β-amyloid protein (known as Aβ protein),

2. Intraneuronal neurofibrillary tangles, comprising filaments of a phosphorylated form of a microtubule-associated protein (Tau).

The key pathogenesis of the Alzheimer's disease (AD) is the alteration in amyloid precursor protein (APP). APP, a membrane protein normally expressed by many cells, including CNS neurons. Aβ40 and 42 are products of proteolytic cleavage formed from APP. Both these proteins aggregate to form amyloid plaques with Aβ42 having more tendency to aggregate than Aβ40. The proteases that cut out the Aβ sequence are known as secretases. Formation of Aβ involves cleavage at two different points, including one in the intramembrane domain of APP, by β- and γ-secretases. γ-secretase is a clumsy enzyme-actually a large intramembrane complex of several proteins-that lacks precision and cuts APP at different points in the transmembrane domain, generating Aβ fragments of different lengths, including Aβ40 and 42. Mutations of the unrelated presenilin genes result in increased activity of γ-secretase, because the presenilin proteins form part of the γ-secretase complex. These different AD-related mutations increase the ratio of Aβ42:Aβ40, which can be detected in plasma, serving as a marker for familial AD. The other reason on the biochemical stage is Tau, the protein of which the neurofibrillary tangles are composed .Their role in neurodegeneration is unclear, although similar 'tauopathies' occur in many neurodegenerative conditions. Tau is a normal constituent of neurons, being associated with intracellular microtubules. In AD and other tauopathies, it becomes abnormally phosphorylated and is deposited intracellularly as paired helical filaments with a characteristic microscopic appearance. When the cells die, these filaments aggregate as extracellular neurofibrillary tangles. It is possible, but not proven, that Tau phosphorylation is enhanced by the presence of Aβ plaques. Tau phosphorylation impairs fast axonal transport, a process that depends on microtubules.

Challenges in drug delivery

The major challenge in the drug delivery remains to be the passage through the blood brain barrier. The blood brain barrier acts as the major barrier for the passage of certain molecules. It acts as a selective filter for the drug molecules. The drug molecules can cross the BBB easily only if they have lipophilic property or by interaction with certain carriers present on the blood brain barrier. The blood–brain barrier (BBB) is presented by the cerebrovascular endothelium sealed with tight junctions. The passage of the molecules could be possible through certain mechanisms such as paracellular aqueous pathway, transcellular pathway, receptor mediated transport

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system, adsorptive mediated transport (Cheng and Liu, 2012). The BBB also has an additional, enzymatic aspect: solutes crossing the endothelial cell membrane are subsequently exposed to numerous degrading enzymes within these cells (Bodor and Buchwald, 2002).

Three cellular elements of the brain microvasculature compose the BBB-endothelial cells:
Astrocyte: These are star-shaped glial cells in the brain and spinal cord, which support the endothelial cells, involved in provision of nutrition and has role in repair and scarring process in case of injury. Astrocytes surround tightly the cerebral microvasculature with their end feet. Partially they are even directly connected to the endothelial cells via gap junctions (Krol, 2012).
Pericytes: These are involved in controlling the flow within blood vessels and between blood vessels and the brain. As contractile cells, they can open or close a given amount to allow (or disallow) certain sized particles to flow through the vessel. Such regulation of blood flow is beneficial to neuronal function because it prevents certain particles in the blood from entering the brain. They are able to phagocytize exogenous protein from the central nervous system and hence can act as cerebral macrophages (Coomber, 1985; Rucker et al., 2000).
Tight junctions (TJs): These are present between the cerebral endothelial cells, form a diffusion barrier, which selectively excludes most blood-borne substances from entering the brain.

The basal lamina is situated between brain capillaries, and the supportive cells and consists of laminin, fibronectin, tenascin, collagens, and proteoglycan. Its function is that of an extracellular matrix providing a scaffold for cell migration, mechanical support for cell attachment, and separation of adjacent tissue (Chen and Liu, 2012). The BBB presents the main obstacle for entrance of large or hydrophilic molecules, microorganisms into the brain. This is true unfortunately also for intentional drug delivery for treatment of a disease (Chen and Liu, 2012).

Overall, the BBB is highly efficient and makes the brain practically inaccessible to lipid-insoluble compounds. Brain-delivery of such compounds, therefore, requires a strategy to overcome the BBB.

APPROACHES IN TREATMENT OF THE ALZHEIMER'S DISEASE-CONVENTIONAL THERAPY

Due to the loss of neuron in the cortex region there is decrease in the amount of the acetylcholine in this region of the brain. There are only five drugs approved by FDA for treatment of Alzheimer's disease which are enlisted in Table 1.

Table 1: Current drugs used for treatment of Alzheimer's disease

Drug Name	Brand Name	Approved For	Year of FDA Approval
Tacrine	Cognex	Mild to moderate	1993
Donepezil	Aricept	All stages	1996
Galantamine	Razadyne	Mild to moderate	2001
Rivastigmine	Exelon	Mild to moderate	2000
Memantine	Namenda	Moderate to severe	2003

Statistics of prevalence of Alzheimer's Disease

In 2006, there were 26.6 million cases of Alzheimer's disease in the world

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(Brookmeyer et al., 2007). It is predicted that by the year 2050, the worldwide prevalence of Alzheimer's disease will grow four-fold, to 106.8 million. It is estimated that 48% of cases worldwide are in Asia, and that the percentage in Asia will grow to 59% by 2050. In U.S currently Alzheimer's disease is the sixth leading cause of death in the United States. One among every nine people above the age of 60 suffers from Alzheimer's disease.

NEED FOR NOVEL APPROACHES OF DRUG DELIVERY SYSTEMS IN TREATMENT OF ALZHEIMER'S DISEASE

With the increasing number of patients being diagnosed with Alzheimer's disease it has become necessary to develop novel delivery systems for the treatment of Alzheimer's disease. Currently available systems are oral drug delivery system such as tablet, capsule, and oral solution. Currently available drugs for treatment are only such that they can slower the progression of the disease and cannot cure it. Unfortunately, medication adherence in Alzheimer's disease is low and good adherence is essential for attempting to slow disease progression and improve or stabilize quality of life. Simplifying treatment regimens and providing more caregiver- and patient-friendly modes of administration that fit in better with daily routines can ease caregiver stress which, in turn, may have a favorable impact on the patient's condition. To overcome problems of medication adherence in the elderly, simple, user-friendly dosage regimens should be prescribed for all medications; thus the need for novel regimens and delivery systems in the pharmacological treatment of Alzheimer's disease. Current oral drug delivery therapy shows side effects such as gastrointestinal disturbances, nausea, vomiting (cholinesterase inhibitors) hence there is requirement of development of delivery system which would be site specific and help reduce the incidences of side effects. In case of Alzheimer's disease drug delivery is to the brain so the delivery system should be such that it can cross the blood brain barrier. As discussed earlier blood brain barrier due to its inherent properties prevents the crossing of certain systems through it. Therefore, various approaches are being studied regarding the brain targeting for Alzheimer's disease, a few are being discussed here:

1. Chemical delivery system
2. Nanoparticles
3. Transdermal patch
4. Vaccines
5. Exosomes

Chemical delivery system (Bodor and Buchwald 2002)

Brain-targeted chemical delivery systems (CDSs) represent a rational drug design approach that exploits sequential metabolism not only to deliver but also to target drugs to their site of action by localizing drugs at their desired site of action, one can reduce toxicity and increase treatment efficiency (Bodor and Buchwald, 1999; Bodor and Brewster, 1991). The CDS concept evolved from the prodrug concept in the early 1980s, but was differentiated by the introduction of target or moieties and the use of multistep activation (Bodor and Brewster, 1982). The CDS is designed to undergo sequential metabolic conversions, disengaging the modifier function(s) and

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finally the target or, after the moiety has fulfilled its site- or organ-targeting role.

Brain-targeting CDSs exploit the fact that if a lipophilic compound enters the brain and is then converted into a hydrophobic molecule, it will no longer be able to exit: it will be 'locked-in'. In principle, many target or moieties are possible for a general system of this kind, but the one based on the 1,4-dihydrotrigonelline to trigonelline system where the lipophilic 1,4-dihydro form (T) is converted in vivo to the hydrophilic quaternary form (T+) proved the most useful. This conversion takes place easily everywhere in the body because it is closely related to that of the ubiquitous NAD(P)H to NAD(P)+ coenzyme system. Because oxidation occurs with direct hydride transfer and without generating highly active or reactive radical intermediates, it provides a non-toxic target or system.

Although the charged intermediate T+-D consisting of the quaternary target or (T+) and drug (D) complex is locked behind the BBB in the brain, it is easily eliminated from the body because of the acquired positive charge, which enhances water solubility. After a relatively short time, the delivered drug D is present only in the brain (as the inactive, locked-in T+-D), providing sustained and brain specific release of the active drug. It has to be emphasized that the system not only achieves delivery to the brain, but also provides preferential delivery; that is, brain targeting.

Nanoparticles

With the aging of the population, drug delivery to the brain for the treatment of neurological disorders (NDs) related to aging remains a challenging task. The conventional drug delivery systems have limited application due to the restrictions posed by the BBB as well as the effects associated with their low bioavailability. Nanotechnology has been explored extensively as an area of potential research for the development of newer therapeutic modalities for the treatment of neurological disorders. Nanotechnology employs engineered materials or devices with size in the nano range (1–100 nm) that are able to interact with biological systems at a molecular level. The enhanced bioavailability and efficacy associated with the formulation of targeted nanoparticles (NPs) of various drugs and bioactive agents used in NDs may provide a possible solution to overcome many of the challenges for the treatment of these diseases.

A concentration gradient due to an increased retention of NPs in the brain blood capillaries combined with an adsorption to capillary walls that would increase the transport of NPs across the endothelial cell layer for drug delivery; solubilisation of endothelial cell membrane lipids leading to membrane fluidization; opening of TJs between endothelial cells thus leading to enhanced permeation of the drug in the nanoparticulate; endocytosis of the NPs by endothelial cells followed by drug release within these cells of the brain; transcytosis of the NPs with bound drug across the endothelial cell layer; inhibition of the P-glycoprotein efflux system by coating the NPs with polysorbate 80 are some of the mechanisms proposed for the penetration of the NPs across the BBB, thus leading to enhanced drug permeability and acceptable therapeutic applications (Lockman et al., 2003). For the efficient and successful transport of therapeutic agents across the BBB, a number of factors have to be considered and optimized, some of which include the molecular weight and the

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structural conformation, the molecular charge, the concentration gradients of the drug, the polymer used, the lipophilicity, the affinity drug, and the dosage form for the receptors (Roney et al., 2005).

Some studies have shown that NPs could be long circulating in the blood and could be taken up by the brain in situ and in vivo with no significant changes in BBB integrity or permeability (Zheng et al., 2002; Lockman et al.,2003; Koziara et al., 2003) .Although, the exact mechanism(s) of transport are not known, the absence of toxicity at the BBB both in vitro and in situ suggests that NPs may be transported through the barrier by endocytosis and/or transcytosis or by passive diffusion in the absence of barrier opening (Zhang et al., 2001). They may be designed to mimic low density lipoproteins and interact with their receptors, thereby triggering uptake by the endothelial cells of the brain (Faraji and Wipf, 2009).

Curcumin has been recently discovered as a potential treatment for AD. This agent acts through several mechanisms including anti-amyloid assembly, anti-oxidant and anti-inflammatory (Amenta, 2001). However, it is found that curcumin is unstable due to rapid hydrolyzation or oxidization. Mulik et al. prepared ApoE3 mediated PBCA (Poly n-butylcyanoacrylate) NPs containing curcumin (ApoE3-CPBCA) to enhance its photostability and cellular uptake (Skaat and Margel 2009). Prepared NPs were characterized for particle size, zeta potential, entrapment efficiency and in vitro drug release. The mean particle sizes of curcumin loaded PBCA NPs (C-PBCA) and ApoE3-C-PBCA were found to be 178 ± 0.59 nm and 197 ± 2.3 with polydispersity indexes of 0.24 and 0.18, respectively. A low polydispersity index is a measure of the uniformity of particle size distribution. As observed by transmission electronic microscopy, the NPs were spherical in shape. The zeta potentials of C-PBCA and ApoE3-C-PBCA were observed to be −28.33 ± 0.16 and −22.44 ± 2.3 mV, respectively, and thus indicated the stable nature of formed particles. X-ray diffraction analysis was done to confirm the entrapment of curcumin inside the NPs. Results on SH-SY5Y neuroblastoma cells indicated higher efficacy of ApoE3-C-PBCA against Aβ-induced cytotoxicity as compared to plain curcumin solution. Anti-apoptotic activity of curcumin was also studied using flow cytometry assays.

From the results of all the experiments conducted, it was concluded that the properties of curcumin were increased with ApoE3-C-PBCA as compared to plain curcumin solution thereby suggesting the enhanced cellular uptake and sustained drug release effect. Besides this, also studied was the synergistic effect of ApoE3 and 21 curcumin because ApoE3 also possesses both antioxidant and anti-amyloidogenic activity (Sahni et al., 2011). It was observed that ApoE3 had activity against Aβ-induced cytotoxicity when used with curcumin. Therefore, the attachment of ApoE3 to C-PBCA NPs clearly increased the uptake of Curcumin into the SH-SY5Y human neuroblastoma cells, with an enhanced activity as compared to plain solution or non-targeted NPs.

Transdermal patch (Kurz et al., 2009)

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. A transdermal drug delivery system has the potential to change the treatment paradigm for many AD patients. Rationale for development of the

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transdermal patch is to improve patient compliance, maintaining the dose. One of the primary objectives for AD treatment with cholinesterase inhibitors is to improve tolerability. Cholinesterase inhibitors that are administered orally can sometimes lead to gastrointestinal side-effects, particularly nausea and vomiting, which may prevent patients from achieving and maintaining optimal therapeutic doses in clinical practice.

Transdermal dermal patch:

- Reduces dosing frequency due to longer duration of action
- Improves bioavailability
- Provides uniform plasma levels, resulting in reduced side effects
- Possibility of terminating the drug administration by simple removal of the patch
- Improves patient compliance via non-invasive, painless, and simple application

The marketed product of transdermal patch for treatment of Alzheimer's disease available is Exelon® transdermal patch by Novartis available in various strengths of 4.5 mg/24 hours, 9.5 mg/24 hours, and 13.3 mg/24 hours.

Vaccines in Alzheimer's disease (Lambracht-Washington and Rosenberg, 2013)

Animal studies show that active or passive immunization against β-amyloid plaques can decrease plaque number and improve cognition. Immunotherapy in AD covers two types of vaccination:

- Active vaccination against Aβ-42 in which patients receive injections of the antigen itself
- Passive vaccination in which patients receive injections of preformed antibodies against Aβ-42.

Studies have suggested that the so formed antibodies crosses the blood brain barrier via receptor mediated transport system as that of the insulin and transferin expressed on the blood brain barrier (Pardridge, 2009).

Mechanism of amyloid-β clearance by amyloid-β-specific antibody which help in removal of the Aβ plaques (Weiner and Frenkel , 2006):

1. One possible mechanism is that there is a direct effect of antibody on β-amyloid, leading to dissolution of amyloid fibrils or neutralization of β-amyloid oligomers. In support of this, direct injection of antibody into the brain causes a decrease in β-amyloid and only antibodies against the N-terminus cause this effect, as has been shown *in vitro* in the presence of β-amyloid and antibody.
2. Second mechanism is that β-amyloid specific antibody leads to Fc receptor (FcR)-mediated phagocytosis of amyloid-β by microglial cell. Consistent with this, following peripheral administration of amyloid specific antibody, activated microglial cells are found surrounding the β-amyloid plaques, and there is less clearance of β-amyloid following injection of amyloid-β-specific antibody in animals that have impaired microglial-cell function compared with wild-type animals.
3. The third mechanism, termed the peripheral sink hypothesis, postulates that administration of β-amyloid specific antibody to the circulation results in a net efflux of β-amyloid from the brain to the plasma.

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Active immunization

For Active immunization AN-1792 (Alzheimers Vaccine, 2006) was studied. Scientists at Elan Corporation developed the treatment based on the theory that administration of β -amyloid might activate the immune system to produce its own anti-amyloid antibodies. Elan and Wyeth-Ayerst Laboratories carried out a collaborative research and development of AN-1792.The vaccine was the first drug targeting β -amyloid to reach clinical trials. In January 2002, Elan and Wyeth-Ayerst Laboratories suspended administration of medication in the Phase IIA trial after four participants who had received multiple doses of AN-1792 developed symptoms of inflammation of the brain and spinal cord. When an additional 11 participants developed these symptoms by the end of February 2002, scientists on the independent Safety Monitoring Committee concluded that no one should be given further doses of AN-1792. Eighteen vaccine recipients (six percent) eventually developed brain inflammation. Scientists followed all trial participants for a year after drug treatment stopped to monitor their health, provide any needed treatment, and gain additional information about the vaccine's safety. The researchers also tracked the drug's effects on memory, thinking and overall function.

Passive Immunization (Sahni et al., 2011)

Various monoclonal antibodies are under different phases of clinical trial are Solanezumab: monoclonal antibody being investigated by EliLilly is in its clinical trial phase. Gantenerumab: monoclonal antibody by Roche. Crenezumab: Crenezumab is a humanized monoclonal antibody that was developed by the Swiss-based biopharmaceutical company AC Immune, licensed the drug to Genentech in 2006, Inc. Its original name RG7412.

The mechanism of action the monoclonal antibodies was found to be that it binds to the amyloid plaques and recruits microglia and macrophages and induced phagocytosis of the amyloid plaques.

Exosomes

Exosomes are natural transport nano-vesicles (40–100 nm) secreted by numerous cell types. These natural nanoparticles are thought to be one of the ways cells communicate with each other and the body's immune system. When exosomes break off from the outer walls of cells, they can take various cellular signals and genetic material with them, transporting this material between different cells. For therapeutic application of the exosomes it would be necessary to isolate the exosome from individual modify it introduce the required exogenous material for therapeutic and re administer the modified exosome.

Lydia Alvarez-Erviti et al obtained the pool of immunologically inert exosomes, harvested bone marrow from inbred C57BL/6 mice with a homogenous major histocompatibility complex (MHC). They purified the exosomes from the culture supernatant by ultracentrifugation. The exosomes obtained were physically homogenous of size 80 nm in diameter 6–12 μg of exosomes (measured based on protein concentration) per 106 cells. To confer targeting capabilities, targeting peptides were fused for muscle and brain, two tissues affected by degenerative diseases amenable to gene therapy, to the extra-exosomal N terminus of murine Lamp2b, a protein found abundantly in exosomal membranes. A peptides—the central nervous system–

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specific rabies viral glycoprotein (RVG) peptide that specifically binds to the acetylcholine receptor,were cloned into Lamp2b. Plasmids encoding the Lamp2b constructs were transfected into the dendritic cells before exosome purification. Lamp2b was strongly expressed in dendritic cells and was incorporated into the dendritic cell–derived exosomes. Expression of the RVG Lamp2b constructs was confirmed by quantitative PCR (qPCR) analysis of transfected dendritic cells. These modifications do not appear to affect the physical properties of the modified exosomes based on electron microscopy of RVG exosomes. Electroporation technique was used to introduce the siRNA into the exoxomes. To study the effect of the exosomes for the treatment of alzhiemers disease 150 μg of each BACE1 siRNA encapsulated in 150 μg of RVG exosomes to normal was injected to C57BL/6 mice and compared the knockdown efficiency to four controls: untreated mice, mice injected with RVG exosomes only, mice injected with BACE1 siRNA complexed to an in vivo cationic liposome reagent and mice injected with BACE1 siRNA complexed to RVG-9R, the RVG peptide conjugated to 9 d-arginines that electrostatically binds to the siRNA3. Cortical tissue samples were analyzed after administration and a significant protein knockdown (45% and 62%) in both siRNA-RVG-9R-treated and siRNA-RVG exosome-treated mice respectively was observed, resulting from a significant decrease in BACE1 mRNA levels. Moreover, they achieved a significant decrease (55%) in the total β-amyloid 1-42 levels, a main component of the amyloid plaques in Alzheimer's pathology, in the RVG-exosome-treated animals. The decrease observed was greater than the β-amyloid 1-40 decrease demonstrated in normal mice after intraventricular injection of BACE1 inhibitors (Alvarez-Erviti et al., 2011). Exosomes display potential for therapeutic delivery of RNAi and in contrast to established liposome formulations, are natural transporter and hence, less likely to exert toxicity or immune responses. In addition, exosomes have the ability to cross biological barriers such as the BBB, as shown in the study using targeted exosomes. The brain-specific RVG peptide recombinantly expressed on the surface of exosomes, was necessary to confer siRNA mediated RNAi responses inside the brain. However, the peptide is not necessarily involved in the transcytosis process across the BBB and this mechanism remains to be fully elucidated (EL Andaloussi, 2013).

FUTURE PERSPECTIVE AND CONCLUSION

With the projected statistic for 2050 for the rise in Alzheimer's disease to be 59% in Asia this area opens a wide array for research and development. All the delivery systems discussed, except for Transdermal patch are yet being studied. This signifies the difficulties in targeting the brain by crossing the blood brain barrier. Hence, there is requirement of even more extensive research and development to be done. With current available drugs Alzheimer's disease progression can only be slowed down also the dose of the drugs are very high which leads to side effects. However, positive responses were seen in the animal studies with respect to treatment by targeting the β-amyloid plaques. Hence, certain delivery systems such as nanoparticles can be further studied for its specific targeting which may act as a carrier. With vaccines being in the clinical trials have also shown a hope for treatment of the disease. Development and designing of new drug delivery system for Alzheimer's disease become very essential.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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